LACTONES FROM EPOXIDES AND ACETOACETIC ESTER

by

Roy M. Adams
B.A., Sterling College, 1940
M.A., University of Kansas, 1942

Submitted to the Department of Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Advisory Committee:

C. A. VanderWerf
Chairman

J. O. Maloney

Jacob Kleinberg

Paul W. Gilles

August, 1949

ACKNOWLEDGEMENTS

The author wishes to express his appreciation for the counsel and direction of Dr. C. A. Vander Werf, who suggested the present investigation, to the American Chemical Society for a predoctoral fellowship which helped to finance this study, and to his beloved wife for her faithful encouragement, and especially for the typing of this manuscript.

TABLE OF CONTENTS

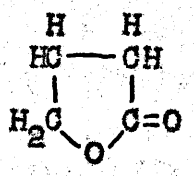
PART I

INTRODUCTION AND HISTORICAL REVIEW

Lactones were first encountered by the early chemists in their investigations of natural substances. The earliest mention of a compound which later proved to be a lactone appears to be the isolation of terebic acid (beta-carboxylic-acid-gamma-isocaprolactone) by Rabourdin (1) from the oxidation of turpentine with hot nitric acid. Other early encountered lactones were valerolactone (2), among the products from the destructive distillation of wood, and the angelica (3) and gluconic lactones, in the study of the sugars (4).

In 1874 the Russian chemist Saytzeff (5) was studying the reduction of succinyl chloride with sodium amalgam in ether and acetic acid, and obtained a substance which had the molecular formula of succinaldehyde, but which he demonstrated must be "an anhydride of gamma-hydroxybutyric acid". This was the first synthesis and the first proof of structure of a lactone. At about the same time Fittig (6) was working with terebic acid and recognized that it was an anhydride of a hydroxy acid. Much earlier Gay-Lussac Pelouze (7) had observed the product formed by the thermal dehydration of lactic acid and had called it lactide. For several years Fittig referred to terebic acid as a "lactide-like anhydride". When Henry's proof that lactide had double

the previously supposed molecular weight (8) was brought to Fittig's attention, he suggested the name "lactone" for the new type of anhydride, and the name has remained for cyclic internal esters (9). The Geneva conference on organic nomenclature adopted the suffix "olid" for lactones (10). The International Union of Chemistry did not specifically modify this term, but stated that "as few changes as possible will be made in nomenclature universally adopted" (11). European publications use the "olid" terminology to some extent, but it is practically absent in American publications.

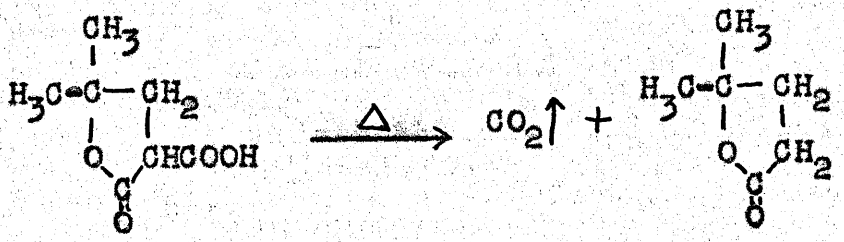


gamma-butyrolactone

4-butanolid

lactone of 4-hydroxy butanoic acid

Fittig assumed that lactones were formed by beta hydroxy acids and lactides by alpha hydroxy acids. Erlenmeyer, Sr. attacked this idea and suggested that the lactones were likely from gamma hydroxy acids containing a five membered ring like succinic anhydride (12). Bredt, a student of Fittig's, settled the question in the same year with the proof that pyroterebic acid was gamma-isocaprolactone (13).



terebic acid

pyroterebic acid
gamma-isocaprolactone

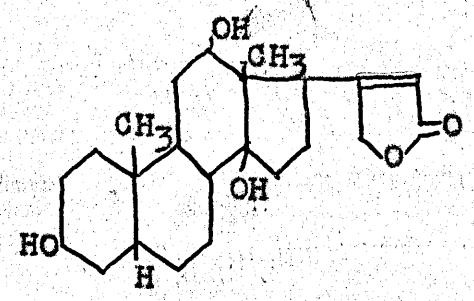
A final explanation of the greater stability and ease of formation of gamma-lactones awaited the Van't Hoff-LeBel theories of the tetrahedral carbon atom (14), and the Baeyer ring strain theory (15). Since the sum of four tetrahedral carbon valence angles of 109° 28' and one oxygen valence angle of 105° (16), equalling 543°, is almost exactly the theoretical 540° for the sum of the internal angles of a planar five sided ring, gamma-lactones, as would be expected, are extremely stable. As these two theories also indicate, delta-lactones are quite common but slightly less stable. Delta-lactones are slowly opened by cold water while gamma-lactones are not (17).

Other lactone types are known. A four membered ring beta-lactone was made from gamma-(o-nitrophenyl)-gamma-bromopropionic acid in 1883 (18). Recently beta-lactones have been made readily by the condensation of ketene and aldehydes (19). Many of the higher membered

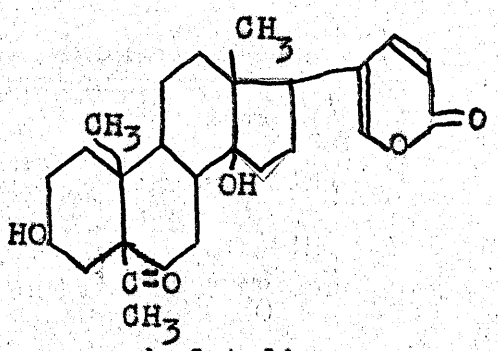
lactone rings, particularly those containing fifteen carbons or more, are found in the musk odors and are of importance to the perfume industry (20).

Lactones were first encountered in the investigation of natural products, and their chief interest to the chemist today lies in the presence of the lactone structure in many naturally occurring compounds exhibiting, not only many diverse types, but also in general, a high degree of physiological activity. The discovery of the lactonic ring in the cardiac glucosides and the demonstration that the lactonic ring was essential to their action on the heart (21) focussed the attention of chemists on the physiological importance of the lactone structure (22, 23, 24, 25).

The cardiac glucosides contain an unsaturated gamma lactone ring attached to a steroid nucleus. The best known aglucone from these glucosides is digoxigenen (26), the aglucone of digitoxine. The toad poisons are chemically closely related to the heart aglucones with an unsaturated delta-lactone (alpha-pyranone) ring replacing the gamma-lactone ring. The best known is bufotalin (27).

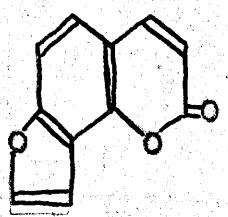


digoxigenin

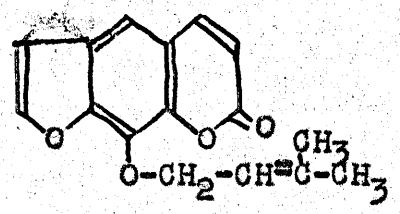


bufotalin

Another group of compounds containing the lactone ring are the furo-coumarin fish poisons, of which the best known are angelican and imperatorin which is toxic to fishes in concentrations of 1 to 100,000 (28).



angelican

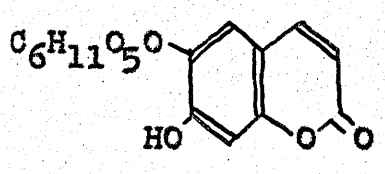


imperatorin

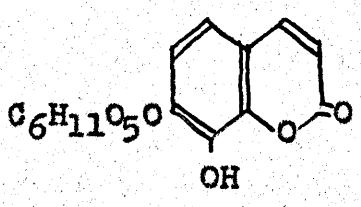
Coumarin is the lactone of cis-o-hydroxycinnamic acid, which is not stable in the free state. However, trans-o-hydroxycinnamic acid is stable and does not form a lactone. Coumarin constitutes the nucleus of a great number of natural substances (29), and has a particularly high distribution coefficient with respect to water and lipids; this accounts for its narcotic properties which are particularly marked in cold blooded animals. It is relatively toxic to higher animals.

Werder (30) attempted to increase the narcotic properties and decrease the toxic properties of coumarin by synthesizing derivatives of coumarin-3-carboxylic acid. The diethyl amide is an excellent sedative.

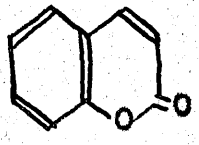
Among interesting phenolic glucosides of coumarin are esculin (31) which absorbs ultra-violet rays and is hence used as a protective agent against sunburn, and daphnin, a very irritating purgative (32).



esculin

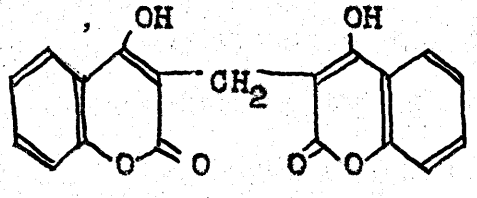


daphnin

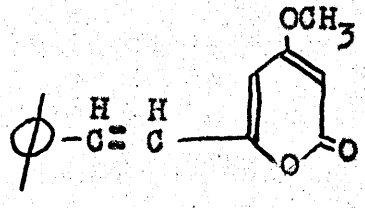


coumarin

Perhaps the best known coumarin derivative is dicoumarol, or antiprothrombin, the compound causing spontaneous hemorrhages in "spoiled sweet clover disease" (33). A vinylog of coumarin is kawain which is an active principle in an ebriating drink prepared by the natives of New Giunea from the Kawa-Kawa root (34).

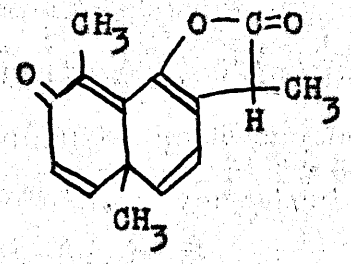


dicoumarol



kawain

Another class of lactones are purgatives. The most important is santonine, the active principle of artemisia buds which have long been used as a vermifuge (35, 36).

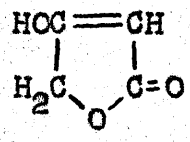


santonine

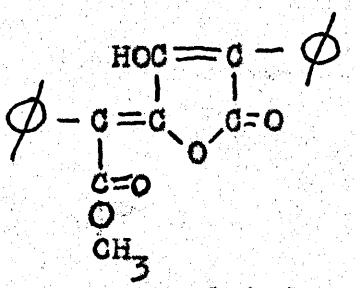
Other familiar substances which act as purgatives are phthalide and phenolphthalein. Rosenmund and Schapiro (37) have prepared synthetic purgatives, substituted butyrolactones, of which gamma-(p-methoxyphenyl)-gamma-butyrolactone is the most active.

Several alkaloids contain a lactone ring (23). In general, the presence of a lactone ring seems to decrease the toxicity and pharmacodynamic properties.

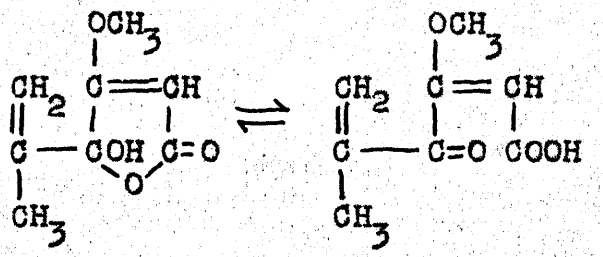
Vulpinic acid, an insecticide (38), and the antibiotics, penicillic acid (39) and clavacin (40) are fungus produced substances, or mycoins. They are three of many mycoin derivatives of tetronic acid. Penicillin itself is a lactam; i.e. a nitrogen analog of a lactone (41).



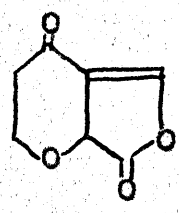
tetronic acid



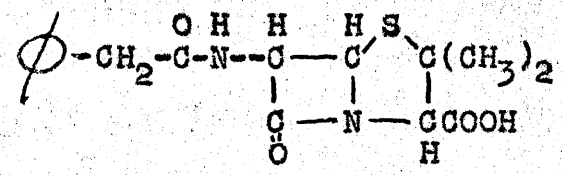
vulpinic acid



penicillic acid

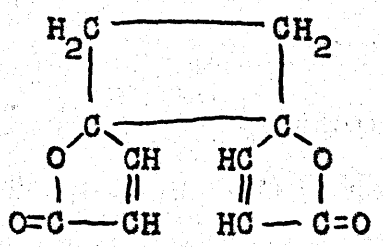


clavacin



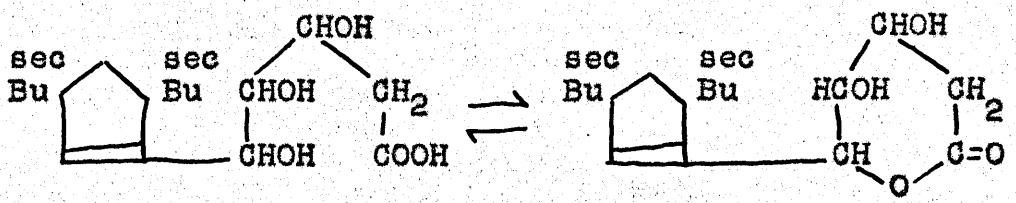
benzyl penicillin

Anemonin is an anticatarrhal and sedative, and also has bactericidal properties (42).



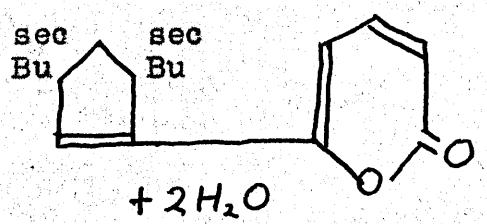
anemonin

The auxines are alcohol-acids which exist in equilibrium with their lactones, which are unstable to light and form lumiauxins. According to Kögl (43), the auxines stimulate plant growth, whereas lumiauxin is inactive. Veldstra and Havinga (44) hold the viewpoint that lumiauxin is a growth inhibitor and that the auxines are inactive. At any rate, auxines are found on the shady side of a plant and lumiauxins on the sunny side.



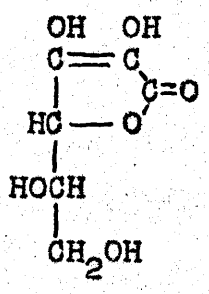
auxine α ⇌ lactone

auxine ↓ light ; ↑ dark

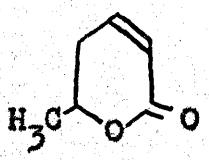


lumiauxin

Vitamin C (l-ascorbic acid) and the growth inhibitor parasorbic acid are relatively simple lactones (45).



l-ascorbic acid



parasorbic acid

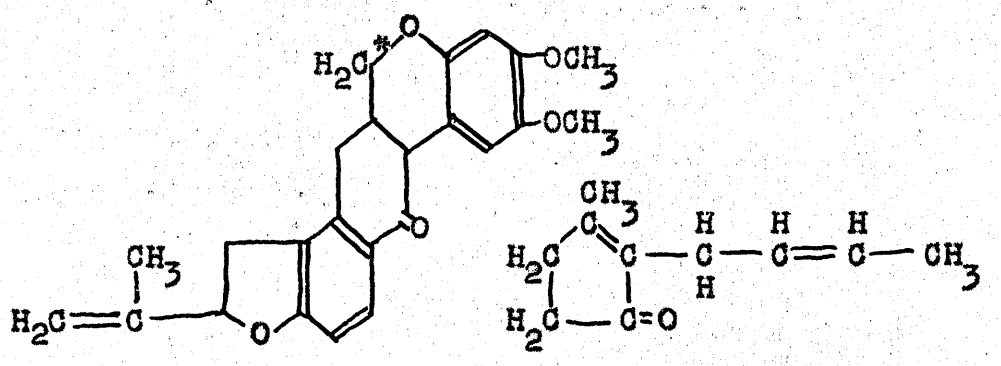
Several workers have attempted to explain the activity of lactones. The work of Medawar on parasorbic acid initiated one line of study. Medawar isolated parasorbic acid from malt extracts and then synthesized it from aldol and malonic ester. He found that this compound was a differential growth inhibitor. It inhibited the growth of mesenchym (or structural) cells but did not influence the growth of epithelian (or skin type) cells. Since vitamins, hormones, and antibiotics must exhibit differential growth effects, such a discovery was bound to create interest. Kuhn (46) confirmed Medawar's discovery and investigated the effect of structurally similar unsaturated lactones. Coumarin was found to be ten times as active as parasorbic acid in inhibiting the growth of cress seeds. All of his compounds were found also to inhibit the growth of yeast and of some types of bacteria. Much earlier Cameron (47) and Sigmund (48) had shown that

coumarin and its derivatives inhibited germination. Macht and Kranz (49) in 1927 published a method for quantitative determination of digitalis glucosides based on their inhibitory action on the growth of the foots of germinating seeds.

Veldstra and Havinga investigated the effect of such substances on monomolecular lecithin and oleate films. While naphthalene-acetic acid, a growth accelerator, tends to open such films, coumarin exerts a condensing action (24). Since protoplasmic membranes are similar lipophilic systems, Veldstra suggested that the coumarin acted by decreasing the permeability of the cell membrane to the passage of water and nutritious matter dissolved in it (51). Veldstra and Havinga also noted that all the growth inhibitors known were unsaturated lactones. They investigated a large number of unsaturated lactones and found that all alpha, beta-unsaturated lactones were growth inhibitory toward cress seeds.

About the same time Lauger, Martin, and Müller (52) showed that several substances containing a double bond conjugated with a carbonyl group were excellent insecticides; e.g. rotenone, and cinerolone, the active principle in pyrethrum. Rotenone is readily oxidized to an

alpha, beta-unsaturated lactone at the starred position.



rotenone cinerolone

Geiger and Conn (53) carried the chemical investigation further, and showed that both clavacin and penicillic acid react quantitatively with the sulfhydryl group of cysteine. Working on the principle that both these compounds were alpha, beta-unsaturated ketones, they synthesized several ketones and tested them as antibiotics. The only synthetic one found to have marked bactericidal properties was acrylophenone. Cavallito and Haskell (54) agreed that cysteine can inactivate both clavacin and penicillic acid, but also pointed out that the activity of both was also dependent upon the lactonic ring since the activity was lost when the ring was opened. The effect of the angelica lactones on the isolated frog heart was shown to be due to peroxide formation (55). The question is still unanswered completely, but the marked diffusibility of

lactones at aqueous-lipid boundaries, their effect on the permeability of these boundaries, and the reaction of alpha, beta-unsaturated lactones with protein sulfhydryl groups are certainly contributing factors in their physiological activity.

Epoxides are compounds containing a three membered carbon, carbon, oxygen ring. The oldest and best known is ethylene oxide (oxirane, epoxyethane). Wurtz prepared this compound by dropping ethylene chlorohydrin on hot concentrated potassium hydroxide in 1859 (56).

The reaction of (a) halohydrins with strong bases is still the most widely used method for preparing epoxides (57). Other methods include:

(b) the use of olefins and peracids. The use of perbenzoic acid as an epoxidizing agent is known as the Prileshajew reaction (58).

(c) the passage of olefins and air over a finely divided silver catalyst (59).

(d) the reaction of dihalides with sodium oxide or silver oxide (60).

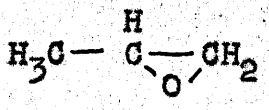
(e) the reaction of hydrogen peroxide with alpha, beta-unsaturated ketones to give alpha-ketoepoxides (61).

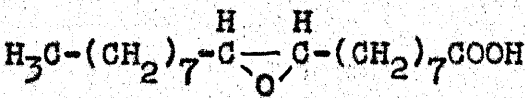
(f) the reaction of ketones and alpha-haloesters to give glycidesters (alpha, beta-epoxyesters) (62).

(g) the reaction of phenacyl halides and aryl aldehydes to yield alpha-ketoepoxides (63).

The nomenclature of epoxides is, like that of lactones, not uniform. The established nomenclature

seems to be that of the oxide of the parent olefin. The Ring Index of the American Chemical Society, in cooperation with the International Union of Chemistry (64), recommends naming as derivatives of oxirane for simple epoxides, and as epoxy derivatives of more complex compounds,





propylene oxide
methyl oxirane

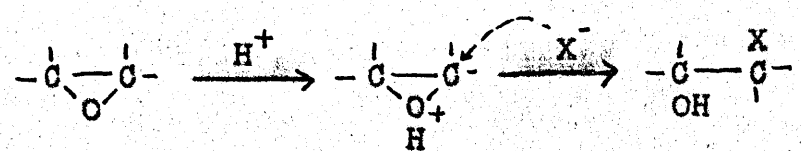
9,10-epoxy-stearic acid

The epoxides used in this study were propylene oxide (methyl oxirane), butadiene monoxide (vinyl oxirane), and styrene oxide (phenyl oxirane). Propylene oxide was first prepared by Krassuski (65) in 1902 by method (a) from propylene chlorohydrin and powdered potassium hydroxide. Butadiene monoxide was similarly prepared by Pariselle in 1910 (66) from beta-bromoethyl-ethylene oxide. Styrene oxide was made by the same method in 1905 from 1-phenyl-2-iodo-ethanol (67). The preparation of styrene oxide by method (b) is in Organic Syntheses (68). Butadiene monoxide has also been prepared by this method (69).

These three epoxides were chosen to produce desired lactones, and also to throw some light on the mechanism

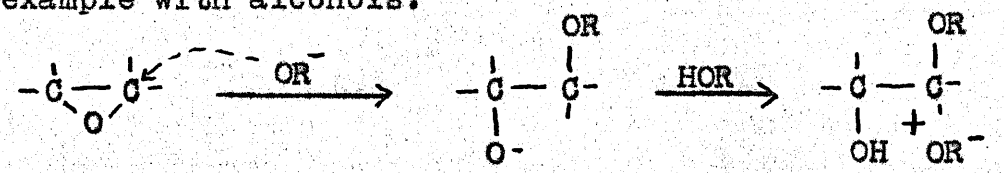
of epoxide ring opening, especially the effect of substituent groups on the direction of ring opening. Epoxide ring formation and opening are of special interest because optical configuration is usually retained (70). The opening of epoxides of cyclic olefins has also been demonstrated to be a "trans" process (71, 72).

Epoxide carbon atoms are electrophilic in character, although not as strongly so as carbonyl carbon. Their reaction with electron donating or nucleophilic groups is often catalyzed by either acids or bases. Winstein (70) has proposed a mechanism for the acid catalysis, assuming the attack of a proton on the epoxide oxygen with the formation of an oxonium ion. The epoxide ring is then ruptured by the attack of a nucleophilic group at the rear of an epoxide carbon, causing nucleophilic displacement of the epoxide oxygen.



The base catalyzed mechanism (73) is considered to be the attack of the conjugate base of the adding substance, at the rear of an epoxide carbon displacing the epoxide

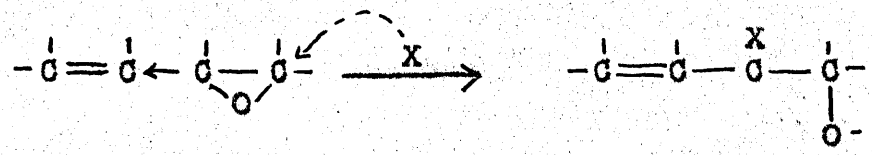
oxygen to form a new anion, which immediately reacts with the adding substance by protolysis to form a neutral addend and another conjugate base anion. For example with alcohols:



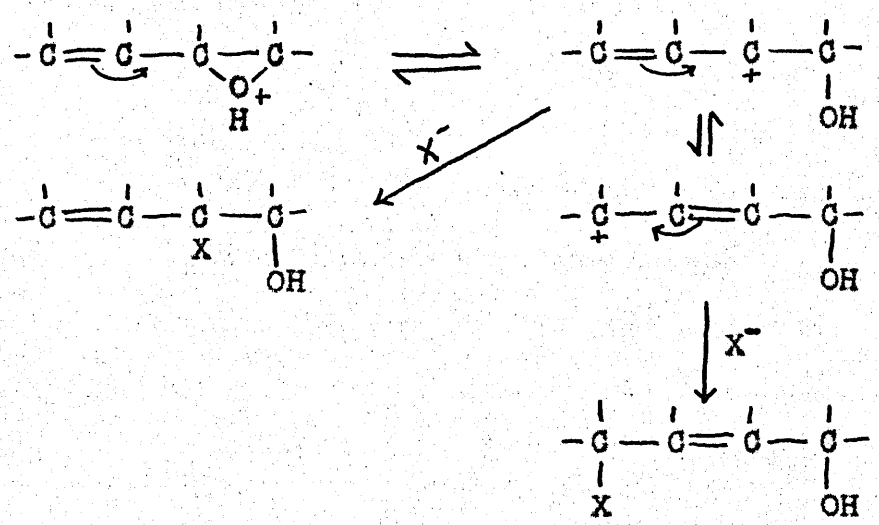
In either case the mechanism is an S_N2 nucleophilic displacement and would be accompanied by inversion of the reacting carbon atom.

It would be expected with either mechanism that the nucleophilic group would attack the carbon with the lower electron density. The methyl group is known to have an electron releasing (74) or +I effect (75). With propylene oxide one would then expect attack at the terminal carbon by the nucleophilic group, and such is either predominantly or entirely the case in all reported examples (76).

Ingold (75) stated that the phenyl and vinyl groups were both more electronegative than hydrogen and exerted a -I effect. On this basis styrene oxide and butadiene monoxide would be expected to yield chiefly products resulting from the reaction of the attacking nucleophilic group at the secondary carbon.



For the acid catalyzed reaction, another mechanism has been suggested for these two epoxides (73, 77). Since in either case the epoxide oxygen is allylic, it was proposed that the epoxide ring opened before reaction with the nucleophilic group is an S_N1 type mechanism. The resulting carbonium ion would be stabilized by resonance.



If such is the mechanism, some addition at the terminal vinyl carbon would be expected. Kadesch (73), who used this mechanism to explain his results in the reaction of methanol and butadiene monoxide, using hydro-

chloric acid as the catalyst, reported a small yield of such material without positive identification. Kadesch postulated an electron releasing effect for the vinyl group, and reported that base catalyzed methanol addition yielded solely the product from attack of the methoxide ion at the terminal epoxide carbon, and that the acid catalyzed product was solely from the attack at the secondary carbon, explaining the latter by the S_N1 mechanism. His identification was based largely on physical properties reported by Petrov (78). Bartlett and Ross, attempting to duplicate Kadesch's work, agreed that the acid catalyzed product was a secondary ether, and showed by oxidative degration that the base catalyzed product contained a large proportion of the secondary ether. On the other hand, Russell and Vander Werf (79) found that in the base catalyzed addition of malonic ester was solely at the terminal carbon. Recently, Guss (80) has reported that the phenoxide anion attacks styrene oxide predominantly at the secondary carbon, and Swern (81) has also reported that the alloxide ion attacks butadiene monoxide and styrene oxide predominantly at the secondary carbon. He attributes an electron releasing effect to the vinyl group and accompanies it with an improbable

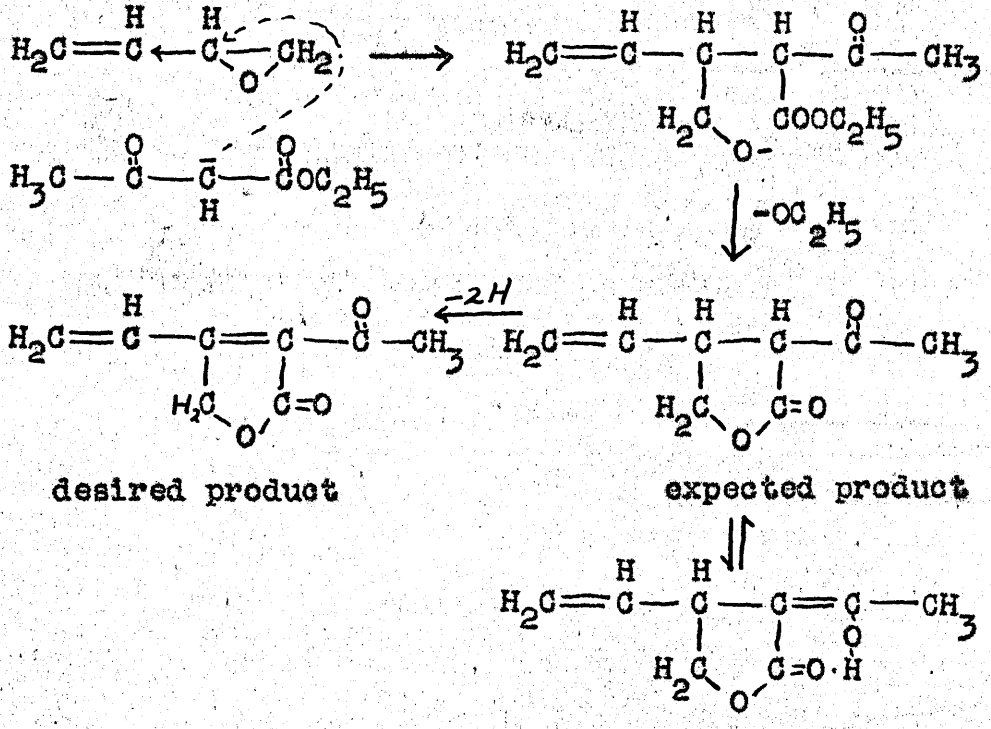
mechanism, suggesting that an allyl alcohol atmosphere weakens the secondary carbon-oxygen bond at the precise moment of attack. He states that the phenyl group may exert either an electron releasing or an electron accepting effect. It should be pointed out that the electron releasing character of the phenyl group is shown only on demand by an electrophilic group. It is difficult to see how a nucleophilic group could demand electrons.

These results indicate the considerable confusion over the inductive effects of the phenyl and vinyl groups, and the reaction products of the two epoxides with bases.

Acetoacetic Ester is the common name for another compound of varied names. Ethyl acetoacetate is about as common, while the I.U.C. name is ethyl 3-ketobutanoate. It was first made by Geuther (82) as early as 1863 by refluxing ethyl acetate with sodium, which is essentially the method used today. Claisen adapted the method to other esters and the condensation now bears his name (83). The compound's early fame came from the discovery and isolation of its ketonic and enolic forms by Knorr (84). It is known today for the ease of addition of alkyl radicals to the methylenic carbon, for the Knoevenagel type condensation with aldehydes at the methylenic carbon (85), and for the ease of cleavage of its derivatives into derivatives of acetone or acetic acid as desired.

The reaction of epoxides with acetoacetic ester seemed particularly worthwhile because the lactones formed would have the alpha-acetyl group to afford additional conjugation. Clavacin and penicillic acid, the two most active lactonic antibiotics known, and acrylophenone, the most active of Geiger and Conn's synthetic antibiotics (53), have not only an alpha, beta-unsaturated carbonyl grouping, but also at least a four fold conjugated system in each case. In the

enol form, the alpha-acetolactones formed from epoxides and acetoacetic ester would have the alpha, beta-unsaturated carbonyl grouping; but it should enhance the activity greatly if an alpha, beta double bond could be inserted in the lactone ring, and if the lactone could be then substituted with a conjugated side chain at the beta position. Since, according to Ingold (75), both the vinyl and phenyl groups have a -I effect, their base catalyzed reaction with ethyl acetoacetate should lead to the desired type of compound, with only the alpha, beta double bond missing.



desired product

expected product

enol form

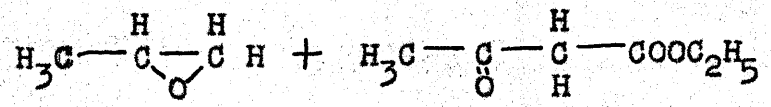
The reported reactions of epoxides with acetoacetic ester include epichlorhydrin (86), cyclohexene oxide (87), and ethylene oxide (88). In only the latter case was a respectable yield obtained. In the present work propylene oxide, styrene oxide, and butadiene monoxide were condensed with acetoacetic ester in good yields and degradations necessary to prove structure were carried out.

It should also be mentioned that these lactones may be useful synthetic intermediates. Acetobutyrolactone has been used in the synthesis of vitamin B_1 (thiamin) (89) and of several synthetic antimalarials (90).

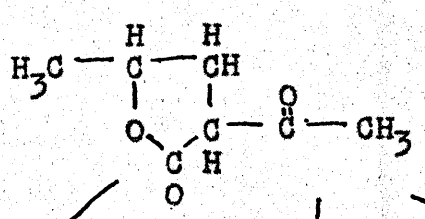
PART II

EXPERIMENTAL

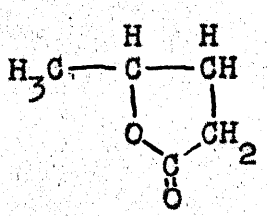
A. PROPYLENE OXIDE AND ACETOACETIC ESTER



(61.4%) 1. NaOEt 2. HOAc

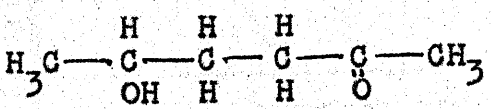


(15.5%) 1. $NaO(CH_3)_3$ 2. HCl

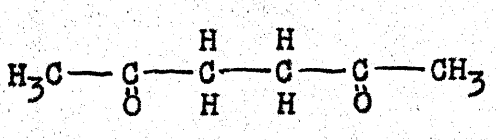


Valerolactone (identified as the hydrazide)

(69%) 5%HCl

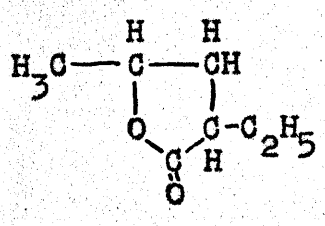


(61%) $Na_2Cr_2O_7$ H_2SO_4



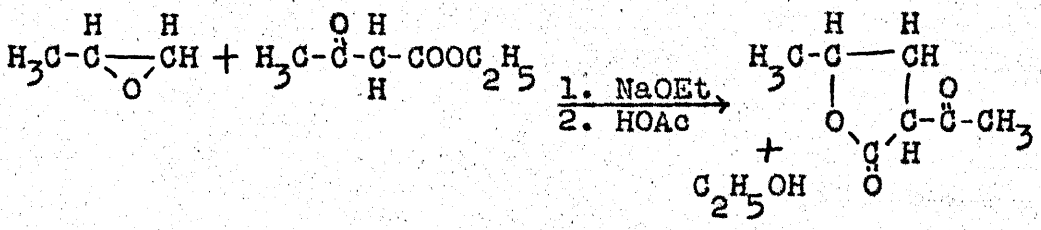
Acetonyl Acetone (identified as the semicarbazone and the 2,4-dinitrophenyl-hydrazone)

H_2NNH_2 KOH



(probable; not isolated)

The Reaction of Propylene Oxide and Ethyl Acetoacetate



(58.08) (130.13) (142.15)

(290 grams) (650 grams) (436 grams)
(5.00 moles) (5.00 moles) (3.07 moles)

$$\text{Yield} = \frac{436}{731} \times 100\% = 61.4\%$$

Into a 5-liter 3-necked flask, equipped with a reflux condenser fitted with a calcium chloride tube, and cooled in a cold water bath, was distilled 2 liters of absolute ethanol prepared by the method of Lund and Bjerrum (91). To the cold alcohol was added 108 grams (4.7 gram atoms) of sodium in large chunks. Use of finely divided sodium involved either extra exposure of the solution to air, or too rapid reaction. Allowing the alcohol to boil during the solution of the sodium resulted in lowered yield. A mercury sealed crescent shaped stirrer was inserted, and the sodium was dissolved by stirring overnight.

The flask was then packed in ice and equipped with a calibrated dropping funnel through which 635 milliliters (650 grams, 5.00 moles) of ethyl acetoacetate was added rapidly. Propylene oxide (methyl

oxirane) (350 milliliters, 290 grams, 5.00 moles), previously chilled in a dry ice chest, was then added dropwise with stirring over a period of 30 minutes.

The mixture was allowed to stir overnight while it warmed to room temperature. The reflux condenser was then removed and arranged for distillation, with a 2-liter 2-necked flask, packed in ice, as a receiver. The 5-liter flask was fitted with a thermometer reaching down into the solution, and the alcohol was removed at less than 100 millimeters. If the still pot temperature was not kept below 50° until nearly all the alcohol has been removed, the yield was drastically decreased. The recovered alcohol always had a little odor of ethyl acetate, but was satisfactory for further runs after treating with magnesium ethoxide (91) or sodium and diethyl phthalate (92).

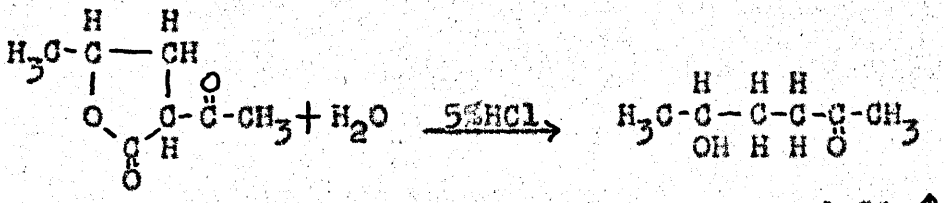
The syrupy residue was decomposed with 300 milliliters (315 grams, 5.25 moles) of glacial acetic acid and 300 grams of ice. The excess acetic acid was neutralized with sodium bicarbonate. The supernatant oily layer was taken off and the residue was extracted with ether. The combined extracts were dried over anhydrous sodium sulfate. The material was then distilled from a Claisen flask equipped with a 12 inch Vigreaux side arm. After removal of the ether, some

residual alcohol, and a small forerun of unchanged acetoacetic ester, there was obtained 348 grams of colorless alpha-aceto-gamma-valerolactone, boiling point 87-89° at 2.0 millimeters, plus 88 grams boiling at 89-92° for a total yield of 436 grams (3.07 moles, 61.4% of the theoretical yield).

A midcut sample for analysis and physical properties was taken at 118-119° and 8 millimeters; d_4^{25} 1.1013, n_D^{25} 1.4489. This and subsequent analyses were performed either by Oakwold Laboratories, Alexandria, Virginia or Clark Microanalytical Laboratories, Urbanna, Illinois.

Analysis: Calculated for $C_7H_{10}O_3$: C, 59.1; H, 7.0.
Found : C, 58.9; H, 7.0.

<u>Decarboxylation of Alpha-aceto-gamma-valerolactone to Hexanol-5-one-2</u>



(142.15)

(100 grams)
(0.70 mole)

(116.16)

(56 grams)
(0.48 mole)

$$\text{Yield} = \frac{56}{81.5} \times 100\% = 69\%$$

In a 500 milliliter flask equipped with a reflux condenser, 100 grams (0.70 mole) of alpha-aceto-gamma-valerolactone was warmed to 70° on the steam bath with 50 milliliters of 12 N hydrochloric acid and 250 milliliters of distilled water, and then allowed to cool with the steam shut off while carbon dioxide was evolved for the next three hours. Continued heating at temperatures above 50° caused formation of a dark supernatant oil insoluble in water and in 5% hydrochloric acid. The mixture was then neutralized and saturated with potassium carbonate. The supernatant layer was taken off, and the aqueous residue was extracted with ether. The combined extracts were dried over anhydrous potassium carbonate and distilled. After removal of solvent, there was obtained at 10 millimeters 56 grams (0.48 mole, 69% of the theoretical yield) of hexanol-5-one-2, boiling at 78-82°. Perkins and Stenhouse (93) obtained hexanol-5-one-2 in 6% yield from the hydrolysis of the condensation product of propylene dibromide with acetoacetic ester, and reported the product as being 2-methyl-pentanol-1-one-4, boiling at 140-142° at 100 millimeters. In a similar run our product distilled at 130-134° and 100 millimeters. Lipp and Scheller (94) repeated the reaction proving the product to be

hexanol-5-one-2, boiling at 80-81° and 10 millimeters. A sample for analysis and physical properties was taken at 2 millimeters and 61°; n_D^{25} 1.4312, d_4^{25} 0.9626. Samples taken at higher pressures and temperatures were all too high in carbon content and too low in hydrogen. Lipp and Scheller (94) and Wohlgemuth (95) both reported similar difficulties with gamma-ketoalcohols, blaming loss of water through dihydrofuran formation. Perhaps dimer formation is involved (96). Wohlgemuth obtained his analytical samples by allowing the furan formed to evaporate out in a dessicator and analyzed the residue.

Analysis: Calculated for $C_6H_{12}O_2$: C, 62.1; H, 10.3.
Found : C, 62.1; H, 10.3.

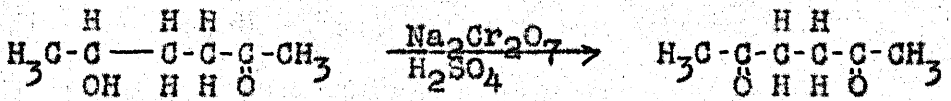
Semicarbazone:

The semicarbazone was very slow to form, but did so after it was warmed for 10 minutes in a steam bath, chilled in ice, and scratched to induce crystallization. It was recrystallized from water, absolute alcohol, and again twice from water, then dried overnight and recrystallized from water; melting point 151.0-151.5°; reported 149-150°. This and subsequent melting points are corrected.

Analysis: Calculated for $C_7H_{15}O_2N_3$: N, 24.3.
Found : N, 24.7.

Attempts to prepare the phenyl urethane gave only symmetrical diphenyl urea.

Oxidation of Hexanol-5-one-2 to Hexandione-2,5 (Acetonyl Acetone)



(116.16) (114.14)

(40 grams) (0.34 mole) (24.0 grams) (0.21 mole)

$$\text{Yield} = \frac{24.0}{39.3} \times 100\% = 61.0\%$$

In a 500 milliliter 3-necked flask equipped with reflux condenser, dropping funnel, mechanical stirrer, and packed in ice, 40 grams (0.34 mole) of hexanol-5-one-2, previously mixed with 50 grams of ice and 75 milliliters of 12 N sulfuric acid, was added dropwise to 34 grams (0.11 mole) sodium dichromate. After the reaction had ceased to be strongly exothermic, it was warmed on the steam bath for 15 minutes, then left overnight.

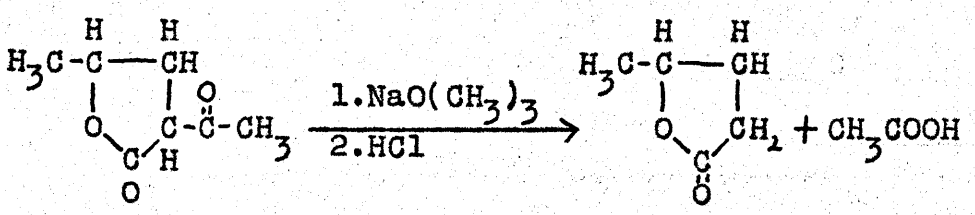
The mixture was neutralized with sodium carbonate and distilled with steam until no more oil separated from saturated potassium carbonate solution. The residue was acidified with sulfuric acid and extracted with ether. The extracts were dried over sodium sul-

fate and distilled, yielding nothing boiling over 100°. The expected product, if any alpha-aceto-beta-methyl-butyrolactone had been formed in the condensation of propylene oxide with ethyl acetoacetate, would be alpha-methyl levulinic acid, boiling point 153-156° at 3 millimeters (97). The distillate was saturated with potassium carbonate and extracted with ether. The extracts were dried over sodium sulfate. After removal of solvent, the residue yielded 24.0 grams (0.21 mole, 61% of the theoretical yield) of hexane-dione-2,5 (acetonyl acetone), boiling at 186-192°; n_D^{25} 1.4222, reported n_D^{25} 1.4232 (98).

Dioxime: melting point 136.2-136.9°, reported 137° (94).

Bis-2, 4-dinitro-phenylhydrazone: melting point 255.8-257.0°, reported 257° (99).

<u>Cleavage of Alpha-aceto-gamma-valerolactone with Sodium-tertiary-butoxide to Gamma-valerolactone</u>



(142.15) (100.11)

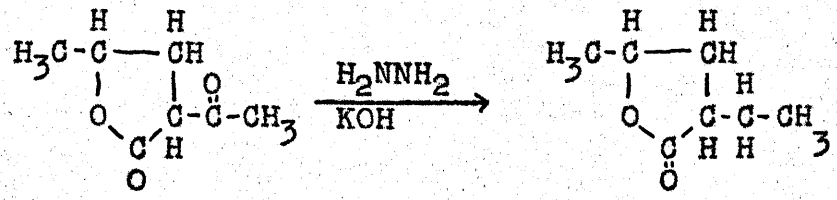
(28.4 grams) (0.20 mole) (3.1 grams) (0.03 mole)

$$\text{Yield} = \frac{3.1}{20.0} \times 100\% = 15\%$$

In 150 milliliters of tertiary butyl alcohol, freshly distilled over sodium, was dissolved 9.6 grams (0.10 mole) of sodium-tertiary-butoxide and 28.4 grams (0.20 mole) of alpha-aceto-gamma-valerolactone. The mixture was refluxed with exclusion of moisture for 24 hours, and was then made neutral to litmus with 12 N hydrochloric acid. The precipitated salt was filtered off, and the residue distilled. After removal of the tertiary butyl alcohol at atmospheric pressure, distillation of the residue at 1.0 millimeter yielded 3.1 grams (0.03 mole, 15% of the theoretical yield) of the lactone of 4-hydroxy-pentanoic acid (gamma-valerolactone) at 51-52°; n_D^{25} 1.4312, reported n_D^{25} 1.4301 (100), and 2.0 grams (0.014 mole, 7% recovery) of alpha-aceto-gamma-valerolactone at 90-95°; n_D^{25} 1.4492, plus considerable gummy residue. An authentic sample of gamma-valerolactone boiled at 51-52° and 1.0 millimeter and gave the same solid derivative for mixed melting point.

Derivative: Gamma-hydroxy-n-valeric-hydrazide, melting point 64.5-65.0°, reported 65° (101).

Wolff-Kishner Reduction of Aceto-valerolactone



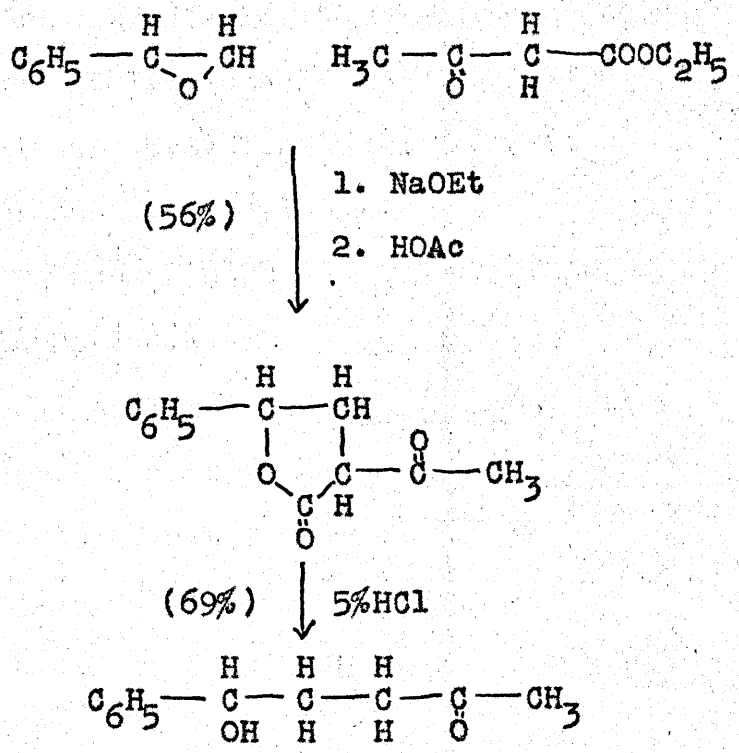
(142.15) (128.16)

(33 grams)
(0.23 mole) (?)

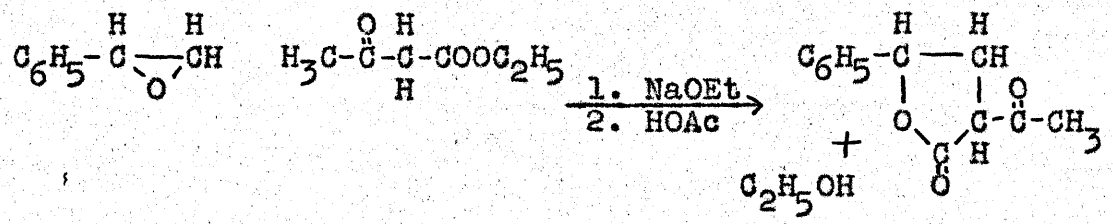
In a 500 milliliter 3-necked flask equipped with thermometer, reflux condenser mounted above a takeoff adapter, and a dropping funnel, 33 grams (0.23 moles) of alpha-aceto-valerolactone was added to a solution of 30 grams (0.535 mole) potassium hydroxide and 20 milliliters (20.6 grams, 0.41 mole) of hydrazine hydrate in 200 milliliters of diethylene glycol. There was a marked heat of reaction. After one hour of refluxing at 140°, the temperature was run up slowly to 180° by taking off water. No oil was present in the water; so no hexanol was formed. It had been thought that decarboxylation and reduction might both occur under the Wolff-Kishner conditions. After refluxing 6 hours at 180°, the reaction mixture was cooled. An equal volume of water was added and the mixture was neutralized with 12 N hydrochloric acid. No oil separated. A continuous ether extraction was tried with

no success. Distillation at atmospheric pressure caused decomposition and fractionation at reduced pressure was unsuccessful. Recorded normal boiling points are 226° for alpha-ethylvalerolactone (102) and 240-250° for diethylene glycol (103). The above procedure is based on the Huang-Minlon adaptation of the Wolff-Kishner reaction (104).

B. STYRENE OXIDE AND ACETOACETIC ESTER



The Reaction of Styrene Oxide and Ethyl Acetoacetate



(120.14) (130.13) (204.22)

(168 grams) (230 grams) (166 grams)
(1.40 moles) (1.77 moles) (0.81 mole)

$$\text{Yield} = \frac{166}{286} \times 100\% = 58.0\%$$

Into a 2-liter 3-necked flask equipped with a reflux condenser and calcium chloride tube was distilled 750 milliliters of absolute ethyl alcohol. The flask was cooled in a cold water bath and 39 grams (1.7 gram atoms) of sodium was added. A mercury sealed crescent shaped stirrer was inserted and stirring was started. After the sodium had largely dissolved and was reacting very slowly, 225 milliliters (230 grams, 1.77 moles) of ethyl acetoacetate was run in at such a rate as to keep the sodium steadily reacting until it had all dissolved. After complete solution of the sodium, the remaining ester was added rapidly.

To the mixture at room temperature was added dropwise with stirring, 160 milliliters (168 grams, 1.40 moles) of styrene oxide (phenyl oxirane). Since the

normal boiling point of styrene oxide is 192°, it was unnecessary to precool the oxide. The reaction was slightly exothermic and was kept near room temperature by the water bath.

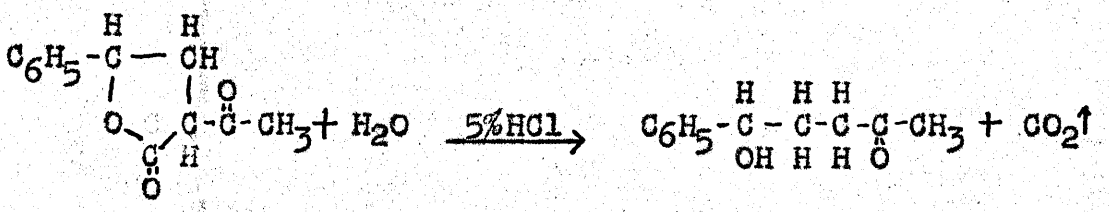
After stirring overnight the stirrer was removed. The condenser was arranged for distillation. The water bath was heated to 50°, and the alcohol was removed under the reduced pressure of a water aspirator. The syrupy residue was decomposed with 500 grams of an ice-water slurry and 120 grams (2.0 moles) of glacial acetic acid. The excess acid was neutralized with sodium bicarbonate, and the supernatant layer separated. The aqueous residue was extracted with benzene. The combined extracts were dried over anhydrous sodium sulfate. The solvent and residual moisture were removed by distillation at atmospheric pressure and at the reduced pressure of an aspirator from a steam bath. After a small forerun of unchanged acetoacetic ester, there was obtained 166 grams (0.81 mole, 58.0% of the theoretical yield) of pale yellow alpha-aceto-gamma-phenyl-gamma-butyrolactone boiling at 146-162° at 1.2 to 1.5 millimeters. In several runs the pressure always fluctuated somewhat during the final distillation, indicating some decomposition. In one case some dehy-

droacetic acid solidified in the condenser. This was identified by its melting point 109° (105) and by the preparation from it of 2,6 dimethyl pyrone by boiling with concentrated hydrochloric acid, giving the reported melting point of 132° (105).

A sample for analysis and physical properties was taken by molecular distillation at 127-128° and 0.15 millimeter; n_D^{25} 1.5395, d_4^{25} 1.1772.

Analysis: Calculated for $C_{12}H_{12}O_3$: C, 70.6; H, 5.9.
Found : C, 70.6; H, 5.8.

Decarboxylation of Alpha-aceto-gamma-phenyl-gamma-butyrolactone to 1-Phenyl-pentanol-1-one-4



(204.22)

(100 grams)
(0.49 mole)

(178.22)

(50.0 grams)
(0.28 mole)

$$\text{Yield} = \frac{50.0}{87.3} \times 100\% = 57.3\%$$

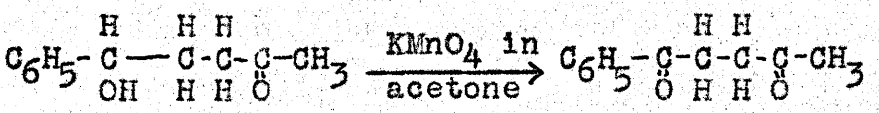
In a 500 milliliter erlenmeyer flask, 100 grams (0.49 mole) of alpha-aceto-gamma-phenyl-gamma-butyrolactone was dissolved in 200 milliliters of absolute alcohol. To the solution was added 100 milliliters of

6 N hydrochloric acid and the mixture was stirred mechanically on the steam bath at 40-50° for 24 hours, after which time no carbon dioxide evolution was evident. The alcoholic layer was salted out with potassium carbonate, separated, and dried over sodium sulfate. After removal of the alcohol there was obtained 50 grams (0.28 mole, 57% of the theoretical yield) of pale yellow 1-phenyl-pentanol-1-one-4, boiling range 125-129° at 1 millimeter. Redistillation for an analytical sample at 0.25 millimeter and 109° left at least 30% of the material in the distillation flask as a clear yellow gum which was perhaps a dimer (96). The gum readily dispersed to an oil in 5% hydrochloric acid. The analytical specimen had these physical properties: n_D^{25} 1.5311, d_4^{25} 1.1000.

Analysis: Calculated for $C_{11}H_{14}O_2$: C, 74.1; H, 7.9.
Found : C, 74.1; H, 7.4.

The product gave a negative iodoform test and no semicarbazone.

Oxidation of 1-Phenyl-pentanol-1-one-4 to 1-Phenyl-pentandione-1,4 (Phenacyl Acetone)



(178.22) (176.21)

(19.7 grams) (0.11 mole) (8.1 grams) (0.046 mole)

$$\text{Yield} = \frac{8.1}{19.5} \times 100\% = 42\%$$

Exactly 19.7 grams (0.11 mole) of freshly prepared 1-phenyl-pentanol-1-one-4 was dissolved in 100 milliliters of acetone in a 500 milliliter flask packed in ice. To the solution was added slowly with stirring, 20 grams (0.13 mole) of potassium permanganate and 0.5 gram of sodium hydroxide dissolved in 100 milliliters of acetone and 200 milliliters of water. The solution was allowed to warm to room temperature overnight, and then acidified with 12 N sulfuric acid and decolorized with sulfur dioxide. The acetone was removed by distillation. The residual mixture was extracted with benzene. The extracts were washed with three 15 milliliter portions of 5% sodium hydroxide solution, and again with 15 milliliters of water. The extracts were dried over sodium sulfate and distilled, yielding 8.1 grams (0.046 mole, 42% of the theoretical yield) of pale yellow 1-phenyl-

pentandione-1,4 (phenacyl acetone), boiling range 106-112° at 0.35 millimeter; n_D^{30} 1.5250.

Derivatives: The semicarbazone formed readily but was unstable to recrystallization; so the following derivatives were prepared by the method of Helberger (106):

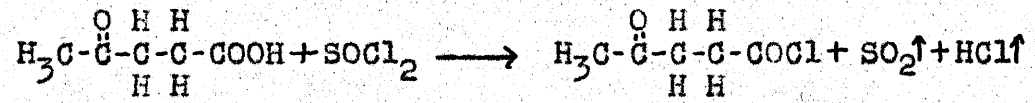
To 2 milliliters of the above product was added 1 milliliter of aniline and the mixture was heated to 125° for 4 hours. The cooled mixture was washed with 6 N hydrochloric acid and recrystallized from alcohol to yield large colorless crystals of 2-methyl-1,5-diphenyl pyrrole, melting point 82.5-83.0° (106) with no depression of mixed melting point with an authentic sample.

Again 1 milliliter of the above product was heated at 150° with 2 grams of phenylene diamine until the mass solidified. The product was washed with hot dilute acetic acid and recrystallized from methanol to give colorless crystals of 2-methyl-5-phenyl-1-(4-amino-phenyl)-pyrrole, melting point 136.8-137.1° (106). No depression of melting point was observed by mixing with an authentic sample.

Neutralization of the basic washings with 12 N sulfuric acid precipitated a solid which, after one recrystallization from water, yielded 2.0 grams (0.016

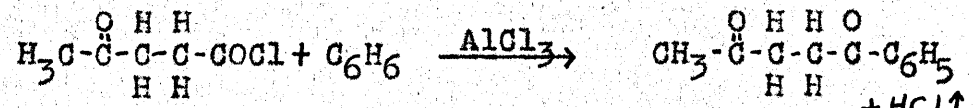
mole, 15% of the theoretical yield) of colorless crystals melting sharply at 122° and giving no depression of mixed melting point with an authentic sample of benzoic acid. The crude material gave no indication of the phenylhydrazone formation which would be expected of alpha-phenyllevulinic acid, melting point 126° (107), the anticipated product if any of the original lactone had been alpha-aceto-beta-phenyl-gamma-butyrolactone.

1-Phenyl-pentandione-1,4 (Phenacyl Acetone) by the Method of Helberger (106)



(116.11) (118.97)

(58 grams) (61 grams) (not isolated)
(0.50 mole) (0.51 mole)



(176.21)

(17.9 grams)
(0.10 mole)

$$\text{Yield} = \frac{17.9}{88.1} \times 100\% = 20.0\%$$

In a 500 milliliter 3-necked flask equipped with reflux condenser, calcium chloride tube, dropping funnel and thermometer, 37 milliliters (61 grams, 0.51 mole) of freshly purified thionyl chloride was added

dropwise to 51 milliliters (58 grams, 0.5 mole) of freshly distilled levulinic acid. The mixture was warmed to 60° to complete the reaction. Then, at a constant temperature of 60°, the pressure was reduced to 40 millimeters to remove any traces of sulfur dioxide and hydrogen chloride.

To the residue was added 100 milliliters of benzene, followed by a suspension of 140 grams of anhydrous aluminum chloride in 300 milliliters of benzene. The benzene was "chemically pure" and had been freshly washed with concentrated sulfuric acid. The suspension was added from a 500 milliliter erlenmeyer flask through a piece of large rubber tubing fitted over the neck previously holding the dropping funnel. The first addition was too large and resulted in a violent reaction with some loss of material. The remaining suspension was added over the course of one hour. The mixture was then held at 50° for one hour and let stand overnight.

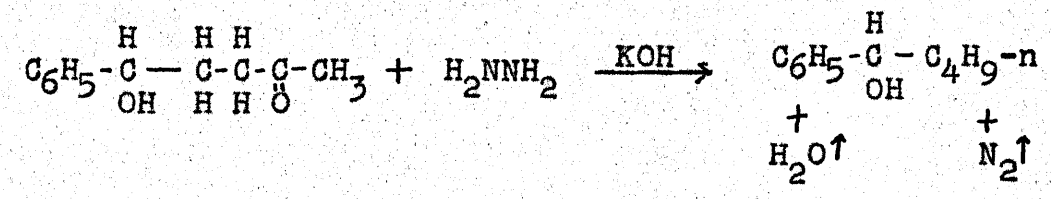
The mixture was decomposed with 500 milliliters of ice and 100 milliliters of concentrated hydrochloric acid. The benzene layer was separated and the aqueous residue extracted with benzene. The combined extracts were washed with four 25 milliliter portions of 5% sodium hydroxide. The aluminum hydroxide formed

was filtered off. The extracts were then distilled. After removal of solvent there was obtained 17.9 grams (0.101 mole, 20.3% of the theoretical yield) of pale yellow phenacyl acetone boiling at 105-106° and 0.3 millimeter; n_D^{30} 1.5235.

This material also gave an unstable semicarbazone. The derivatives with aniline and p-phenylene diamine were used for comparison with those of the previous experiment.

Helberger reported that phenacyl acetone was a bright yellow solid melting at 29°. Neither this product nor that of the previous experiment could be induced to solidify after one week in the ice box.

Wolff-Kishner Reduction of 1-Phenyl-pentanol-1-one-4 to 1-Phenyl-pentanol-1 (Phenyl Butyl Carbinol)



(178.22) (50.06) (164.24)

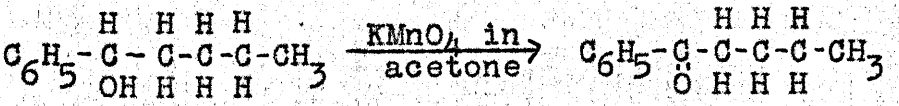
(46.9 grams) (36 grams) (35.8 grams)
(0.263 mole) (0.72 mole) (0.218 mole)

$$\text{Yield} = \frac{35.8}{43.2} \times 100\% = 83.0\%$$

In a 1-liter 3-necked flask equipped with thermometer, reflux condenser, and takeoff adapter, 46.9 grams (0.26 mole) of freshly prepared 1-phenyl-pentanol-1-one-

4, boiling range 132-135° at 1 millimeter, was dissolved in 400 milliliters of triethylene glycol immediately after distillation. To the solution was added 35 milliliters (36 grams, 0.72 mole) of 100% hydrazine hydrate and 50 grams (0.89 mole) of potassium hydroxide. The mixture was refluxed overnight. Aqueous liquor was then drawn off until the temperature reached 185°. Refluxing was continued for 4 hours. The solution was then cooled to 40° in an ice bath and an equal volume of water was added. The solution was neutralized with 12 N hydrochloric acid, and the upper layer of oil was separated. The residue was extracted with ether and the combined extracts were dried over anhydrous sodium sulfate. After removal of solvent the product was fractionated through an 8 inch Vigreaux column, yielding 35.8 grams (0.22 mole, 83.0% of the theoretical yield) of phenyl butyl carbinol, boiling at 140-142° at 25 millimeters; n_D^{25} 1.4806, d_4^{25} 1.010; reported boiling point 137° at 21 millimeters (108); n_D, d both unreported.

Oxidation of 1-Phenyl-pentanol-1 to 1-Phenyl-pentanone-1 (Phenyl Butyl Ketone, Valerophenone)



(164.24) (162.22)

(16.4 grams) (0.10 mole) (10.5 grams) (0.065 mole)

$$\text{Yield} = \frac{10.5}{16.2} \times 100\% = 65\%$$

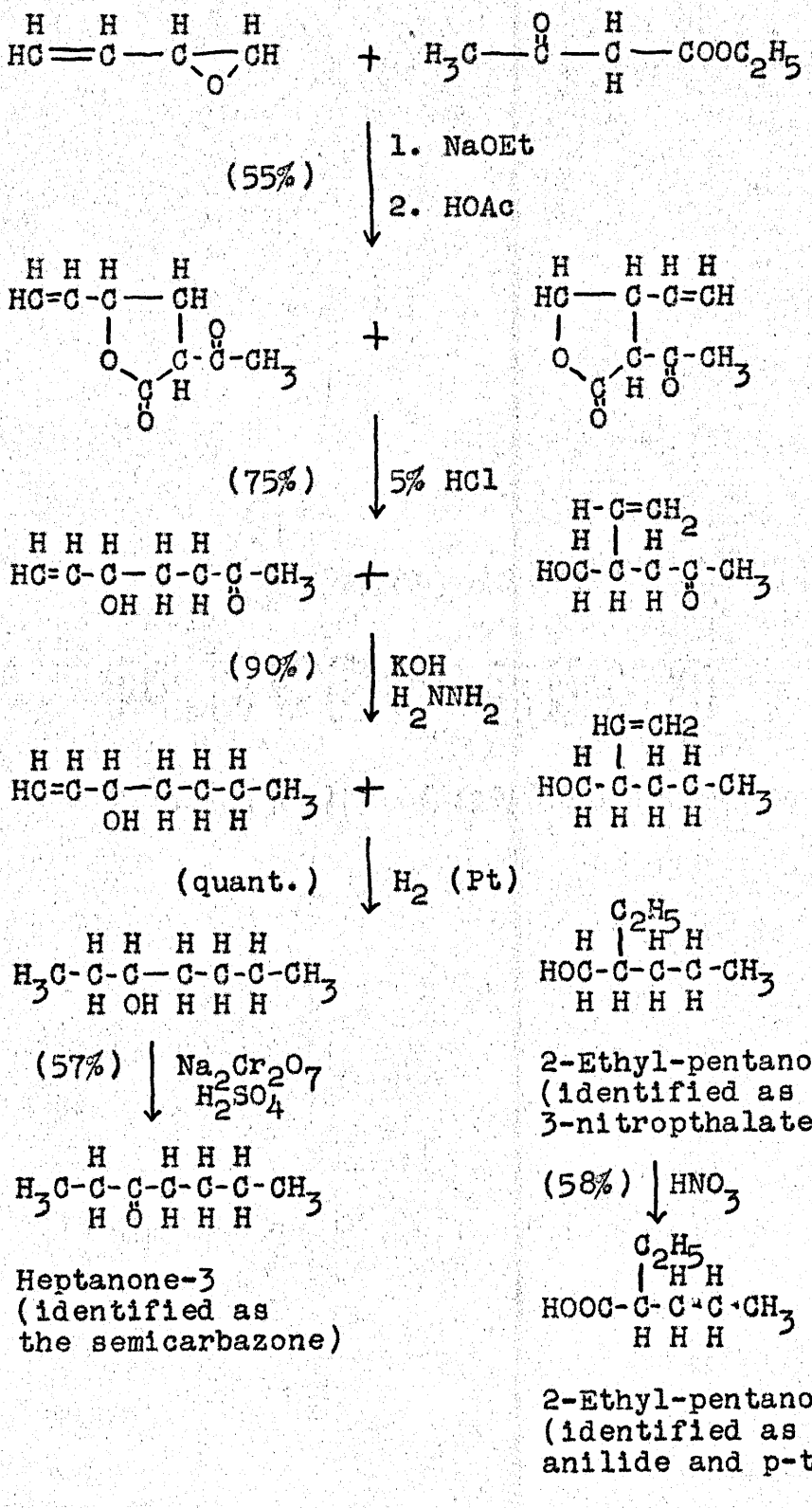
In a 1-liter 2-necked flask packed in ice and equipped with a mechanical stirrer and a dropping funnel, 16.4 grams (0.10 mole) of 1-phenyl-pentanol-1 and 5 grams of potassium hydroxide were dissolved in 50 milliliters of acetone. Potassium permanganate (21 grams, 0.13 mole), dissolved in 400 milliliters of water, was added dropwise with stirring. After the stirred mixture had been allowed to come to room temperature overnight, the precipitated manganese dioxide was filtered off by suction, and the filtrate was acidified and extracted with benzene. The extracts were washed with 5% sodium carbonate solution, dried over anhydrous sodium sulfate, and distilled, yielding at 25 millimeters, 10.5 grams (0.065 mole, 65% of the theoretical yield) of 1-phenyl-pentanone-1 (phenyl butyl ketone) boiling at 135-141°; n_D^{25} 1.5080, d_4^{25} 0.9819; reported boiling point at 25 millimeters

135-140° (109); n_D^{19} 1.5152 (110), d_{20}^{20} 0.988 (109).

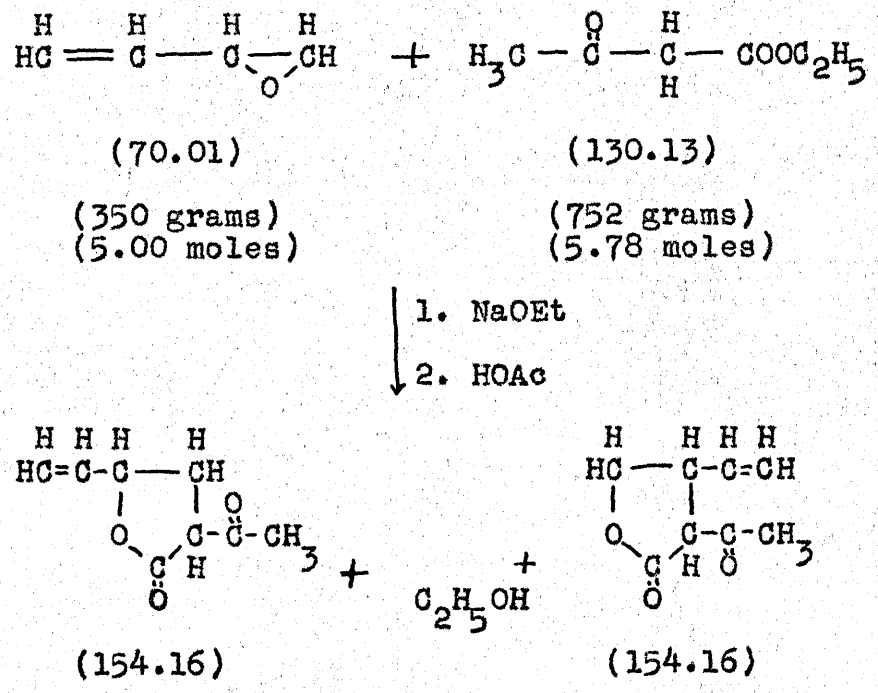
Semicarbazone: melting point 166.5-167.3°, reported 166° (110).

The sodium carbonate washings after acidification yielded 1.6 grams (0.013 mole, 13% of the theoretical yield) of benzoic acid, melting point 122°. Alpha-phenyl-valeric acid, the expected product had any alpha-aceto-beta-phenylbutyrolactone been formed in the reaction of styrene oxide and ethyl acetoacetate, has a melting point of 52° (111).

C. BUTADIENE MONOXIDE AND ACETOACETIC ESTER



The Reaction of Butadiene Monoxide and Ethyl Acetoacetate



(70.01) (130.13)

(350 grams) (752 grams)
(5.00 moles) (5.78 moles)

1. NaOEt
2. HOAc

(154.16) (154.16)

(425 grams)
(2.76 moles)

$$\text{Yield} = \frac{425}{771} \times 100\% = 55.1\%$$

Into a 5-liter 3-necked flask, equipped with reflux condenser fitted with a calcium chloride tube, and placed in a cold water bath, was distilled 2.2 liters of absolute ethanol. To the alcohol was added 133 grams (5.8 gram atoms) of sodium. A crescent-shaped glass stirrer with mercury seal was inserted and stirring was started. After the sodium had dissolved, 735 milliliters (752 grams, 5.78 moles) of ethyl acetoacetate was added rapidly from a calibrated dropping funnel.

The mixture was chilled in ice and 400 milliliters (350 grams, 5.00 moles) of recently distilled, chilled butadiene monoxide was added dropwise with stirring. After about four hours the reaction mixture set to a heavy paste. It was necessary to remove the stirrer to effect vacuum distillation later. In one run a Hershberg stirrer was tried and found to wrap badly. Stirring was continued as long as possible. The reaction of this epoxide was definitely the most exothermic of the three, and the heat of reaction at the center of an unstirred run raised the temperature enough to lower the yield appreciably in one case.

After standing overnight the alcohol was removed by distillation on a steam bath at 40 millimeters pressure. The syrupy residue was neutralized with 350 milliliters (350 grams, 5.84 moles) of glacial acetic acid in a slurry of 500 grams of ice and 1 liter of water. It was necessary to stir the materials together for several hours to react all the syrupy residue. The supernatant layer was separated and the aqueous residue extracted with ether. The combined extracts and product were distilled without drying. After removal of the solvents and a forerun of acetoacetic ester, there was obtained 425 grams (2.76 moles, 55.1% of the theoretical yield) of the mixed product, alpha-aceto-beta-vinyl-

gamma-butyrolactone and alpha-aceto-gamma-vinyl-gamma-butyrolactone, at 88-93° and 2 millimeters. A sample for analysis and physical properties was taken at 78° and 0.5 millimeter; n_D^{25} 1.4714, d_4^{25} 1.1157.

Analysis: Calculated for $C_8H_{10}O_3$: C, 62.4; H, 6.5.
Found : C, 62.4; H, 6.4.

Several attempts were made to fractionate this mixture using a Smith column, a Todd column, and a Piros-Glover column. In the best controlled run on a 1x100 centimeter Todd column packed with 3/32 inch glass helices and mannostatted at 5.0 millimeters, with a 70 gram charge there was obtained at a 30 to 1 reflux ratio:

117 - 117.7°	2.5 grams
117.7°	53.8 grams
117.7° - 120°	4.0 grams
	60.3 grams (86.1% of charge)

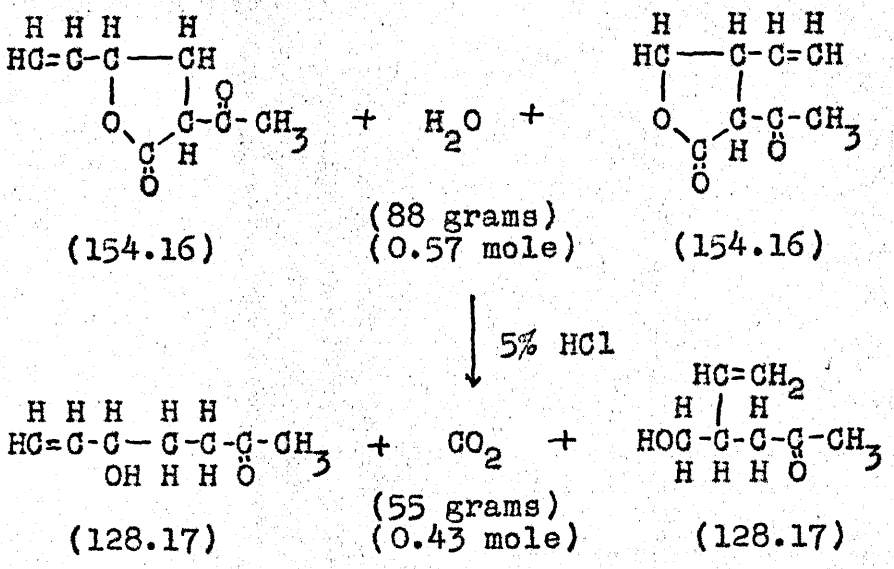
In another distillation, not mannostatted, at approximately 0.5 millimeter, 15 different samples were taken periodically. The index of refraction varied without any correlation from 1.4710 to 1.4716 at 25°.

The largest distillation attempted was through a 1x100 centimeter Smith column packed with ¼ inch glass helices with a 200 gram charge. Degradations were carried out on the first 69.0 grams and the final 30.8 grams including the tailings, which were recovered by distillation without a column. The degradation indi-

cated that the final 30.8 grams were nearly pure alpha-aceto-gamma-vinyl-gamma-butyrolactone; n_D^{25} 1.4710, d_4^{25} 1.1126. The yields and physical properties of the degradation products of this fraction are described in conjunction with the description of the degradation of a typical portion of the mixed lactones. This fraction will be referred to as fraction B.

Attempts were made to separate the 2,4-dinitro-phenylhydrazones of the 2 lactones by chromatography. Both the 2,4-dinitro-phenylhydrazones and the semicarbazones of these lactones form quite readily, but are unstable to recrystallization. Adsorbents tried were anhydrous sodium sulfate, anhydrous magnesium sulfate, Silene EF, talc activated at 300°, and Fisher adsorption alumina. Only the alumina held the hydrazones, and it decomposed them.

Decarboxylation of Alpha-aceto-beta-vinyl-gamma-butyrolactone and Alpha-aceto-gamma-vinyl-gamma-butyrolactone to Hepten-1-ol-3-one-6 and 2-Vinyl-pentanol-1-one-4



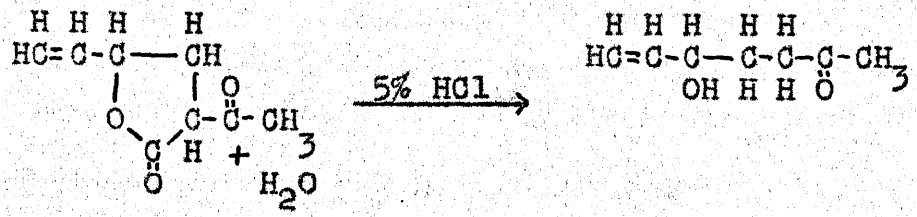
$$\text{Yield} = \frac{55}{73} \times 100\% = 75\%$$

In a 500 milliliter erlenmeyer flask, 88 grams (0.57 mole) of the mixed vinylbutyrolactones were stirred with 250 milliliters of water and 50 milliliters of concentrated hydrochloric acid at 40-50° for 8 hours, after which time the lactones had gone completely into solution, and the evolution of carbon dioxide had ceased. The unsaturated ketoalcohols were then isolated by saturating the solution with potassium carbonate, separating the supernatant layer and extracting the aqueous residue with ether. The combined extracts and product were dried over anhydrous sodium sulfate. After removal of solvent the residue was distilled at

5 millimeters pressure to yield 55 grams (0.43 mole, 75% of the theoretical yield) of hepten-1-ol-3-one-6 and 2-vinyl-pentanol-1-one-4 boiling at 76-78°.

A sample for analysis and physical properties was taken from the midcut of the third immediately consecutive distillation of this material; n_D^{25} 1.4526, d_4^{25} 0.9800.

Analysis: Calculated for $C_7H_{12}O_2$: C, 65.7; H, 9.4.
Found : C, 66.0; H, 9.2.



(154.16) (128.17)

(30.0 grams) (0.26 mole) (20.7 grams) (0.16 mole)

$$\text{Yield} = \frac{20.7}{24.9} \times 100\% = 83\%$$

By the same procedure 30.0 grams (0.26 mole) of fraction B yielded 20.7 grams (0.16 mole, 83% of the theoretical yield) of hepten-1-ol-3-one-6, boiling range 113-114° at 25 millimeters; n_D^{25} 1.4526, d_4^{25} 0.9800.

Dimerization of Hepten-1-ol-3-one-6 and 2-Vinyl-pentanol-1

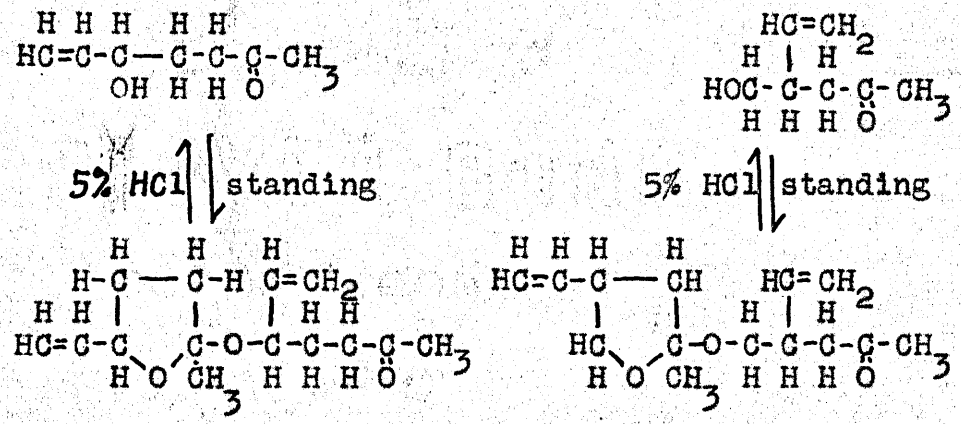
When 55 grams (0.43 mole) of the normal mixture of the gamma-ketoalcohols was allowed to stand overnight and was redistilled, 36 grams (65%) of the product distilled at 107-109° and 5 millimeters. This product was insoluble in water, but dissolved in 5% hydrochloric acid. It added bromine readily, reacted slowly with sodium, gave a very slight carbonyl test with 2,4-dinitro-phenylhydrazine reagent, and no iodoform test.

The product was dissolved in 5% hydrochloric acid and displaced with potassium carbonate. The recovered product and ether extracts of the aqueous layer were distilled, yielding, after solvent removal, 33 grams (92%) boiling at 74-76° and 5 millimeters. A sample of the higher boiling material analyzed as follows:

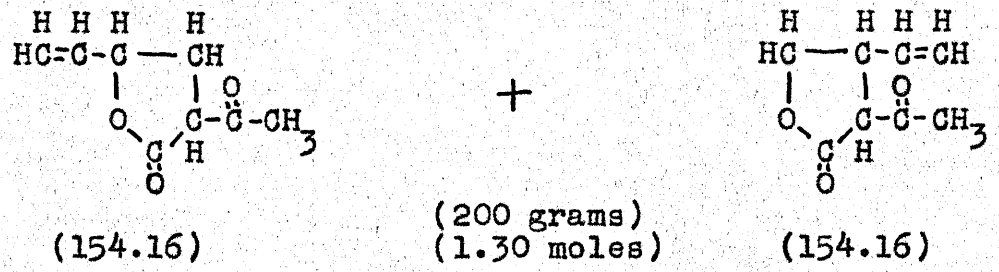
Calculated for $C_{14}H_{22}O_3$: C, 70.5; H, 9.2.

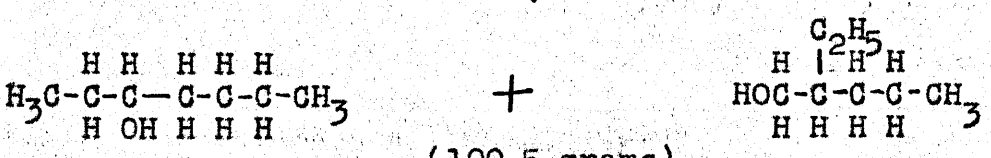
Found : C, 69.6; H, 9.3.

Stevens and Stein (96) found similar phenomena with pentanol-1-one-4 (gamma-aceto-propyl alcohol) and with the 3-chloro and 3-bromo derivatives. The equations that follow give their formulation of the product, although qualitative tests did not support their formulation.



Wolff-Kishner Reduction of Hepten-1-ol-3-one-6 and 2-Vinyl-pentanol-1-one-4 to Heptanol-3 (Ethyl-butyl-carbinol) and 2-Ethyl-pentanol-1





$$\text{Yield} = \frac{100.5}{150.5} \times 100\% = 66.8\%$$

When the labile nature of gamma-ketoalcohols was discovered, further degradations were carried past this stage immediately without purification of the ketoalcohol.

In a 1-liter erlenmeyer flask, 200 grams (1.30 moles) of the mixed vinyl-butyrolactones were stirred overnight with 510 milliliters of distilled water and 90 milliliters of concentrated hydrochloric acid. The next morning a clear, slightly darkened solution remained which was saturated with potassium carbonate. The supernatant layer was separated and immediately added to a 1-liter 2-necked flask, equipped with a thermometer and a reflux condenser mounted above a 250 milliliter Orchin type separatory funnel, and containing 140 milliliters (144 grams, 2.88 moles) of 100% hydrazine hydrate and 140 grams (2.50 moles) of potassium hydroxide. A marked evolution of heat occurred. The flask was heated under total reflux for two hours (at 128°). Reflux was then cut off and the temperature allowed to rise slowly up to 190°. Foaming (evolution of nitrogen) began at 135°. Two layers were formed in the Orchin funnel. The upper layer was separated and the aqueous residue extracted with ether. The combined product and extracts were dried over anhydrous sodium sulfate. Attempts to distill the product at reduced pressure resulted in excessive foaming for 7 hours. Finally the material was filtered through a column of 5 grams of norite and 5 grams of Johns-Mansville Hyflo Super-Cel. The column was washed with two 5 milliliter portions of ether.

The filtrate was then hydrogenated directly over 0.2 gram Adams catalyst, absorbing 70 pounds per square inch after running overnight. An extra 0.05 gram of catalyst was added to insure complete reduction and hydrogenation was continued for 1 hour. No further pressure drop was observed. The catalyst was filtered off and washed with ether. After removal of the ether, distillation at atmospheric pressure yielded 100.5 grams (0.86 moles, 66.7% of the theoretical yield based on the original lactones) of the two heptyl alcohols, boiling at 155-169.5°; n_D^{25} 1.4241, d_4^{25} 0.8238.

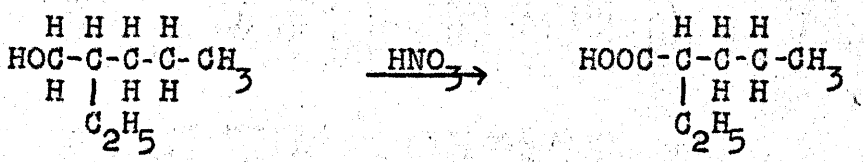
On a 1x100 centimeter Todd column with a 100 to 1 reflux ratio, 70.0 grams of the above material was fractionated at atmospheric pressure (736 millimeters) to yield 25.5 grams, boiling at 155-158°; n_D^{20} 1.4228, n_D^{25} 1.4208, d_4^{25} 0.8165; reported: boiling point 155.9° (112), 152.7-154° (113), 156.5-157° (114), n_D^{20} 1.4222 (112), 1.4201 (113), n_D^{25} 1.4175 (113), d_4^{25} 0.8159 (113). No crystalline derivatives of this alcohol have been reported. Attempts to prepare such a derivative were unsuccessful.

An intermediate fraction of 21.5 grams boiling at 158-164° was obtained, followed by 25.5 grams at 164-166°; n_D^{25} 1.4251, d_4^{25} 0.8296; reported: boiling point

164-166° (114), n_D^{17} 1.428, d_4^{25} 0.832; for the (d) isomer n_D^{25} 1.4250, d_4^{25} 0.8280 (115). 3-nitrohydrogenphthalate: melting range 129.5-130.1°, reported 127-128° (114).

Using a similar procedure, Wolff-Kishner reduction of 20.0 grams (0.156 mole) of the fraction B hepten-1-ol-3-one-6 yielded 16.7 grams (0.144 mole, 90% of the theoretical yield) of hepten-1-ol-3 boiling at 69.5-71.5° and 25 millimeters; n_D^{25} 1.4320, d_4^{25} 0.8306; reported for the 1-isomer n_D^{20} 1.4340, d_4^{20} 0.8360 (116). This product (15 grams) was hydrogenated and then oxidized directly to heptanone-3 without isolation.

Oxidation of 2-Ethylpentanol-1 to 2-Ethyl-pentanoic Acid (Alpha-ethylvaleric Acid)



(116.20) (130.18)

(11.6 grams) (0.10 mole) (7.5 grams) (0.058 mole)

$$\text{Yield} = \frac{7.5}{13.0} \times 100\% = 58\%$$

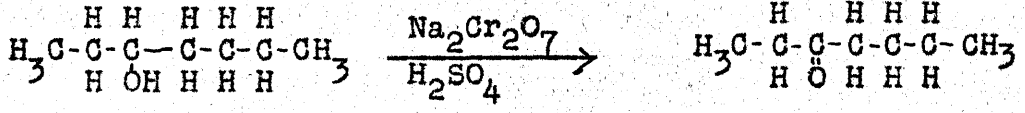
Following the procedure of Powell (117) 31 milliliters (45 grams, 0.71 mole) of nitric acid was placed in a 100 milliliter 3-necked flask equipped with a mechanical stirrer, dropping funnel, and thermometer.

While the temperature was kept at 25-30° by means of an ice bath, 11.6 grams (0.10 mole) of the 164-166° fraction from the distillations of the previous products was added dropwise with stirring. The reaction was allowed to stir overnight, then heated on the steam bath for 1 hour. Stirring was stopped and the upper oily layer separated. The aqueous residue was extracted with ether. The extracts and product were distilled through a Claisen flask with a 12 inch Vigreaux side arm to remove solvents. The residue was distilled at 30 millimeters to yield 7.5 grams (0.058 mole, 58% of the theoretical yield) of 2-ethyl-pentanoic acid (alpha-ethylvaleric acid); n_D^{25} 1.4192, d_4^{25} 0.9110; reported for the d-isomer: n_D^{25} 1.4178, d_4^{25} 0.9080 (115).

Anilide: melting point 93.4-93.8°, reported 94° (118).

p-Toluide: melting point 127.9-128.3°, reported 129° (118).

Oxidation of 3-Heptanol to 3-Heptanone (Ethyl Butyl Ketone)



(116.20) (114.18)

(6.8 grams) (0.059 mole) (3.8 grams) (0.033 mole)

$$\text{Yield} = \frac{3.8}{6.8} \times 100\% = 57\%$$

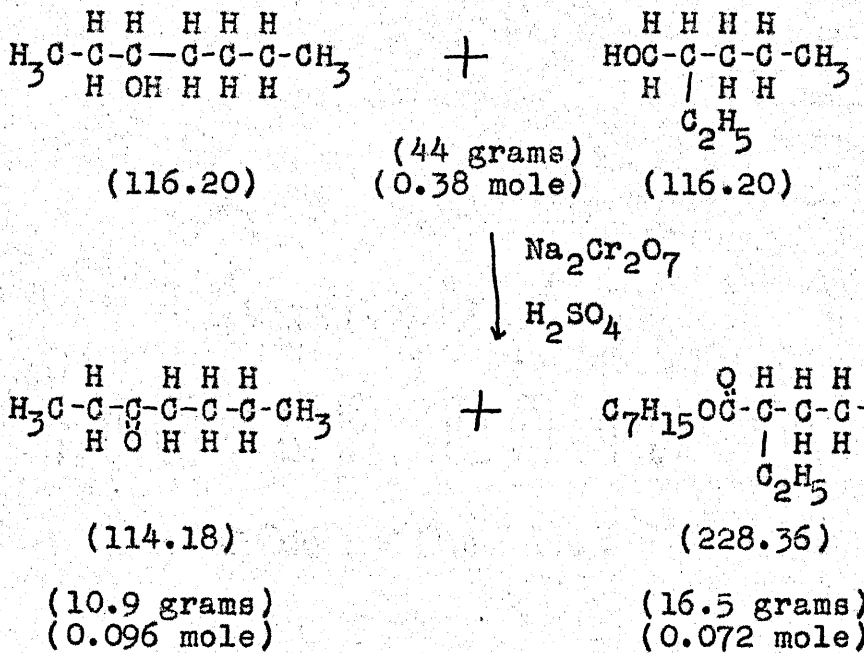
Using the procedure of Sherrill (112), to 7.5 milliliters (6.8 grams, 0.059 mole) of the 155-158° fraction of the distillation in a 200 milliliter 3-necked flask equipped with stirrer and dropping funnel, was added one-half of a solution of 6 grams of sodium dichromate in 80 milliliters of water. To the other half of this latter solution was added 5 milliliters of concentrated sulfuric acid. This remaining solution was then added dropwise to the reaction mixture with stirring. The solution was heated for 1 hour on the steam bath with stirring, and then steam distilled until no more oil came over. The oil was separated, dried over anhydrous sodium sulfate, and distilled at 25 millimeters to yield 3.8 grams (0.033 mole, 57% of the theoretical yield) boiling at 53-58°; n_D^{25} 1.4080 (for reported values see below).

Semicarbazone: melting point 102.5-103.1°, reported 103° (120).

By the same procedure, 15.0 grams (0.13 mole) of fraction B heptanol was oxidized to yield 10.1 grams (0.089 mole, 68% of the theoretical yield) of heptanone-3 boiling at 56.5 to 58° and 25 millimeters; n_D^{25} 1.4076, n_D^{20} 1.4094, d_4^{25} 0.8162; reported n_D^{20} 1.40917, d_4^{20} 0.8183 (112).

Semicarbazone: melting point 102.3-103.0°.

Oxidation of the Normally Mixed Heptyl Alcohols from the Degradation



$$\text{Yield of heptanone-3} = \frac{10.9}{43.2} \times 100\% = 25.3\%$$

$$\text{Yield of ester} = \frac{16.5}{43.2} \times 100\% = 38.2\%$$

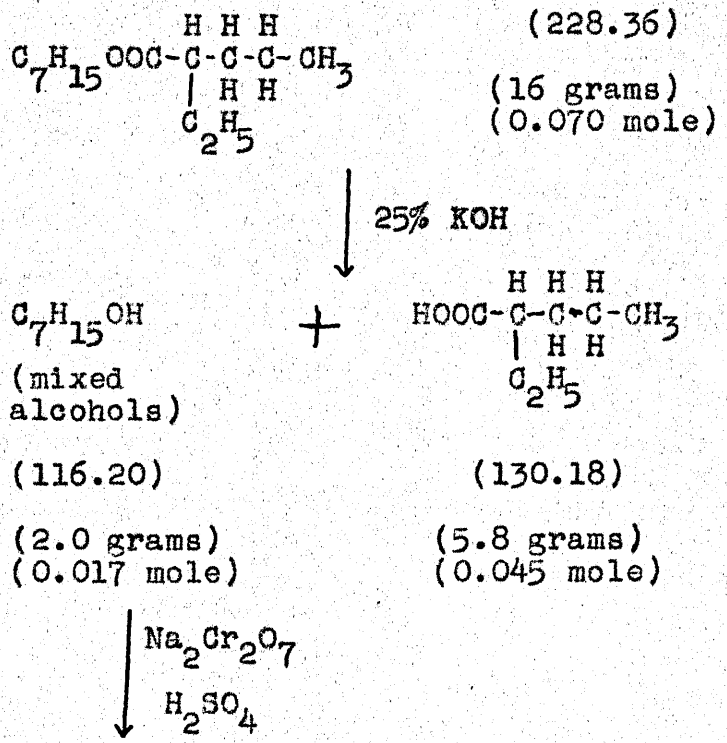
Use of the same oxidation procedure with a mixture of 44 grams (0.38 mole), the unfractionated alcohols

yielded 10.9 grams (0.096 mole, 25% of the theoretical yield) of heptanone-3 and 16.5 grams (0.072 mole, 38% of the theoretical yield of the esters of the two alcohols and 2-ethyl pentanoic acid, boiling at 130-135° and 25 millimeters; n_D^{25} 1.4315, d_4^{25} 0.8591.

Analysis: Calculated for $C_{14}H_{28}O_2$: C, 73.7; H, 12.3.
Found : C, 74.1; H, 11.9.

Variations of this procedure, such as adding the alcohol to the oxidizing mixture, carrying out the reaction at room temperature, and using very dilute acid solutions, gave approximately the same proportions of ketone and ester. Use of acidic permanganate gave similar results. Use of alkaline or neutral permanganate left no high boiling products except a small percent of the recovered alcohols.

Saponification of the Esters



$$\text{Yield of acid} = \frac{5.8}{9.1} \times 100\% = 63.6\%$$

$$\text{Yield of alcohols} = \frac{2.0}{8.15} \times 100\% = 24.6\%$$

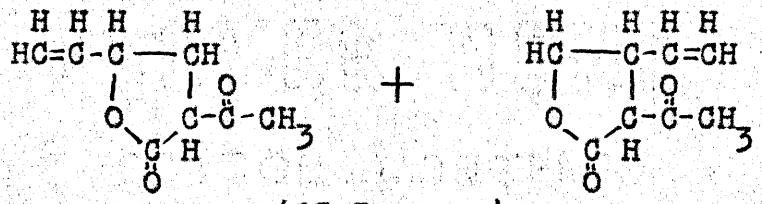
$$\text{Yield of heptanone semicarbazone} = \frac{1.2}{2.95} \times 100\% = 40.8\%$$

In a 200 milliliter, round bottom flask, 16 grams (0.070 mole) of the mixed esters were refluxed for 48 hours with 100 milliliters of 25% aqueous potassium hydroxide. The upper layer was separated from the cooled mixture, and the aqueous residue was extracted with ether. This neutral fraction upon distillation gave at 25 millimeters, 2.0 grams (0.017 mole, 25% of the theoretical yield) of mixed heptyl alcohols at 70-85° and 5.3 grams (0.022 mole, 33%) of recovered ester at 128-136°. The alcohols were oxidized as in the previous experiment and the entire oily layer from the steam distillation was isolated as the semicarbazone. The yield of semicarbazone, melting point 101-102°, was 1.2 grams (0.0070 mole, 41% of the theoretical yield).

The aqueous residue was acidified with 12 N sulfuric acid and extracted with ether. The extracts were dried over anhydrous sodium sulfate and distilled to yield 5.8 grams (0.045 mole, 64% of the theoretical yield) of 2-ethyl pentanoic acid at 111-119.5° and 25 millimeters; n_D^{25} 1.4182, reported 1.4178 (115).

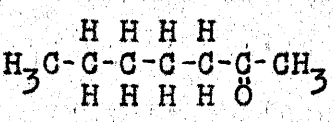
Amide: melting point 102.4-103.1°, reported 102.5-103.5° (119).

Hydrogenation of the Normally Mixed Lactones



(154.16) (95.5 grams) (0.62 mole) (154.16)

(156.18) (73 grams) (0.47 mole) (156.18)



(114.18)

(10 grams)
(0.088 mole)

Yield of saturated lactones = $\frac{73}{96.7} \times 100\% = 75.5\%$

Yield of heptanone = $\frac{10}{70.6} \times 100\% = 14\%$

The mixed unsaturated lactones (95.5 grams, 0.62 mole) were hydrogenated at 50 pounds per square inch over 0.5 gram of Adams' catalyst until 0.62 mole of hydrogen had been absorbed. The catalyst was filtered

off and the product distilled at 25 millimeters yielding at 56-57°, 10 grams (0.088 mole, 14% of the theoretical yield) of heptanone-2; n_D^{20} 1.4152, n_D^{25} 1.4172; reported n_D^{20} 1.4143 (112). An iodoform test was positive.

Semicarbazone: melting point 119.7-120.5°; reported 120° (112).

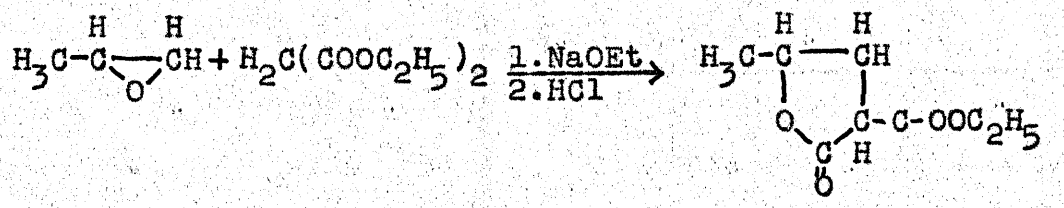
The residue was distilled to yield at 0.7 millimeter and 82-83°, 73 grams (0.47 mole, 76% of the theoretical yield) of a mixture of the lactones of 2-aceto-4-hydroxy-heptanoic acid and of 2-aceto-3-ethyl-4-hydroxy-butanoic acid.

Analysis: Calculated for $C_8H_{12}O_3$: C, 61.5; H, 7.7.
Found : C, 61.5; H, 7.8.

Attempts to fractionate this mixture on the Todd column were unsuccessful.

D. EPOXIDES AND MALONIC ESTER

The Reaction of Propylene Oxide and Malonic Ester



(58.08) (160.17) (172.18)

(116 grams) (320 grams) (215 grams)
(2.00 moles) (2.00 moles) (1.25 moles)

$$\text{Yield} = \frac{215}{344} \times 100\% = 62.5\%$$

Following the procedure of Russell and Vander Werf (79), 46 grams (2.0 moles) of sodium were dissolved in 1300 milliliters of absolute alcohol in a 2-liter 3-necked flask equipped with reflux condenser, calibrated dropping funnel, and mechanical mercury sealed stirrer. To the mixture 310 milliliters (320 grams, 2.00 moles) of malonic ester was added dropwise with stirring, followed by 140 milliliters (116 grams, 2.00 moles) of previously chilled propylene oxide (1,2-epoxypropane) added in the same manner. The mixture became thick enough to stop the stirrer within 2 hours after addition of the oxide was started.

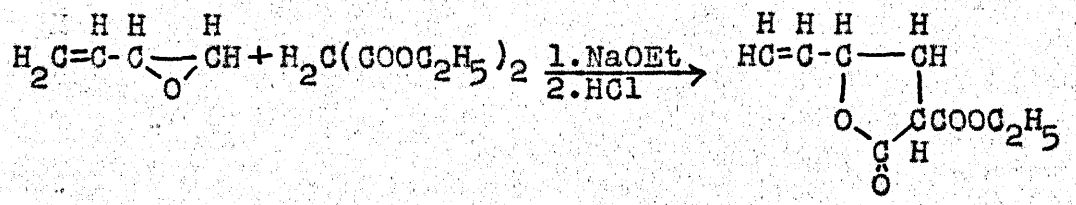
The mixture was heated overnight on the steam bath. It was then cooled and neutralized to litmus with 12 N hydrochloric acid. A heavy precipitate of salt was filtered off. The filtrate was evaporated

under reduced pressure (100 millimeters) until the still pot reached 140°. The residue was pasty and basic to litmus. It was washed with 200 milliliters of water. An oily upper layer separated and was taken off. The aqueous layer was acidified with hydrochloric acid and extracted with ether. The combined extracts were dried over sodium sulfate and then distilled. After removal of solvent, the residue was distilled yielding 75 grams (0.47 mole, 23% recovery) of malonic ester at 58-60° and 1.3 millimeters, and 215 grams (1.25 moles, 62.5% of the theoretical yield) of alpha-carbethoxy-gamma-valerolactone at 85-90° and 0.5 millimeter.

A midcut sample for analysis and physical properties was taken at 1.0 millimeter and 101°; d_4^{25} 1.1227, n_D^{25} 1.4413.

Analysis: Calculated for $C_8H_{12}O_4$: C, 55.8; H, 7.0.
Found : C, 56.2; H, 7.0.

The Reaction of Butadiene Monoxide and Malonic Ester



(70.01) (160.17) (184.19)

(70 grams) (160 grams) (100 grams)
(1.00 mole) (1.00 mole) (0.543 mole)

$$\text{Yield} = \frac{100}{184} \times 100\% = 54.3\%$$

Following the same procedure as in the previous experiment, 23 grams (1.00 gram atom) of sodium, 160 grams (1.00 mole) of malonic ester, and 70 grams (1.00 mole) of butadiene monoxide in 1 liter of alcohol yielded 100 grams (0.54 mole, 54% of the theoretical yield), boiling point 118-120° and 2.3 millimeters; n_D^{25} 1.4560, d_4^{25} 1.1220.

Analysis: Calculated for $C_9H_{12}O_3$: C, 58.7; H, 6.5.
Found : C, 58.8; H, 6.9.

E. PREPARATION OF BUTADIENE MONOXIDE

1. Chlorourea Method

$$2Cl_2\downarrow + 2H_2NCONH_2 + CuCO_3 \rightarrow 2ClNHCONH + CuCl_2 + CO_2\uparrow$$

2(70.91) 2(60.05) (123.58) 2(94.50)(134.48) (44.01)

(240 grams) (247 grams)
(4.00 moles)(2.00 moles)

Gain in weight per mole of chlorourea formed =

$$\frac{2(70.91) - 44.01}{2} = 46.91 \text{ grams}$$

Actual gain in weight = $\frac{187}{46.9}$ = 3.82 moles of chlorourea

$$ClNHCONH + H_2O \xrightarrow{[H^+]} HNCONH + HOCl$$

$$HCCCCH + HOCl \longrightarrow HC{=}C{-}C(OH)(Cl){-}CH$$

(54.09) (52.47) (106.55)

(320 grams) (139 grams)
(5.9 moles) (1.30 moles)

$$\text{Yield} = \frac{139}{407} \times 100\% = 34.2\%$$

Into a slurry of 247 grams (2.00 moles) of cupric carbonate, 240 grams (4.00 moles) of urea, and 500 grams of water, chlorine was bubbled with efficient stirring and at a temperature of 0-5° until a gain in weight of 187 grams (corresponding to the formation of 3.82 moles of monochlorourea) had been observed. The reaction vessel was packed in ice, and dry ice was added when necessary to keep the temperature down.

At the same time 500 milliliters (320 grams, 5.9 moles) of butadiene-1-3 were condensed in a 500 milliliter flask packed in a dry ice-methanol bath.

The chlorourea solution was mixed with a slurry of 3.5 liters of ice and water in a 5-liter 3-necked flask equipped with a mechanical stirrer and an ammonia condenser which was vented through 50 centimeters of mercury. The stirrer seal and bearing was made by fitting the stirrer shaft with rubber stoppers into the plunger of a discarded hypodermic syringe. The seal was lubricated with mineral oil or glycerol. The liquid butadiene was added through the third neck as rapidly as possible, followed by 150 milliliters of glacial acetic acid. This neck was stoppered; all connections were wired down, and stirring was started. After two hours the ice disappeared. After five hours the pressure was released through a three-way stopcock in the vent line and the unreacted butadiene (200 milliliters, 128 grams, 2.4 moles) was recondensed. The mixture was extracted repeatedly with ether. The ether extracts were washed with saturated sodium carbonate. The residue, after removal of solvent, yielded 139 grams (1.30 moles, 34% of the theoretical yield) of butadiene monochlorohydrin (1-chloro-3-buten-3-ol) at 75-85° and 60 millimeters, (reported boiling range

65-68° at 35 millimeters) (73). This product was colored and still had a definite odor of acetic acid. Since this did not interfere with its subsequent use, no further attempt to purify it was made. There was a considerable quantity of dark gummy material left in the distilling flask.

2. Calcium Hypochlorite Method

$$Ca(OCl)_2 + CO_2\downarrow + H_2O + 2HC{\equiv}C{-}C{=}CH$$

(142.99) (44.01)(18.02) 2(54.09)

(215 grams)
(1.50 moles)

(excess)

$$CaCO_3\downarrow + 2HC{\equiv}C{-}C(OH)(Cl){-}CH$$

(100.09) (106.55)

(95.5 grams)
(0.90 mole)

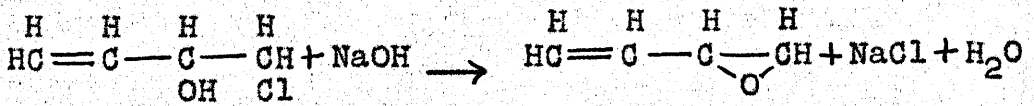
$$\text{Yield} = \frac{95.5}{320} \times 100\% = 29.8\%$$

In 3.5 liters of an ice-water slurry in the previously described apparatus was dissolved 307 grams of Pittchlor (70% calcium hypochlorite, Columbia Chemicals Division of the Pittsburgh Plate Glass Corporation, Pittsburgh, Pennsylvania). The third neck was fitted with a gas inlet tube reaching down to the bottom of

the flask and connected to a tank of butadiene and a carbon dioxide tank. Butadiene was run in until there was steady refluxing (1 drop in 2 seconds) at the ammonia condenser. Carbon dioxide was then admitted at a sufficient rate to cause periodic bubbling (about every 5 seconds) through the mercury. After 1 hour, the reflux was a steady stream; so the butadiene tank was shut off. After 6 hours the carbon dioxide was cut off and the pressure was released. Approximately 150 milliliters (96 grams, 1.8 moles) of butadiene was recovered by condensation.

The precipitate of calcium carbonate was filtered off, and the filtrate was extracted repeatedly with ether. The extracts were dried over sodium sulfate and distilled to yield, at 60 millimeters and 75-85°, 95.5 grams (0.90 mole, 30% of the theoretical yield) of butadiene monochlorohydrin.

Butadiene Monoxide (3,4-Epoxybutene-1)



(106.55) (40.01) (70.01)

(450 grams) (360 grams) (205 grams)
(4.22 moles) (9.0 moles) (2.93 moles)

$$\text{Yield} = \frac{205}{335} \times 100\% = 61\%$$

The following procedure is an adaptation of that of Kadesch (73).

In a 1-liter 3-necked flask fitted with a dropping funnel, thermometer, takeoff condenser, heating mantle, and mechanical stirrer was placed a 50% solution containing 240 grams (6.0 moles) of sodium hydroxide. Butadiene monochlorohydrin (450 grams, 4.22 moles) was added dropwise with stirring while the temperature was maintained at 120-125°. The distillate was collected in a 1-liter flask packed in ice. After all the chlorohydrin had been added, 3 more moles of 50% sodium hydroxide was added and the reaction was warmed to 130°. Heating was stopped. The upper layer of the distillate was separated and dried over calcium chloride. The product was then distilled from a modified Claisen flask with a 12 inch Vigreaux side arm to yield 205 grams (2.93 moles, 61% of the theoretical yield) of butadiene monoxide (3,4-epoxybutene-1) boiling at 67-68°; n_D^{20} 1.4172, n_D^{25} 1.4152, d_4^{25} 0.8712; reported boiling point 65.0-65.8°; n_D^{20} 1.4170, d_4^{20} 0.875 (73).

PART III

DISCUSSION OF RESULTS

Propylene oxide, styrene oxide, and butadiene monoxide were reacted with acetoacetic ester in reasonably good yield. With propylene oxide the expected product, alpha-aceto-gamma-valerolactone was formed. The structure was established by decarboxylation to hexanol-5-one-2 which was identified by derivatization as the semicarbazone. The ease with which gamma-ketoalcohols split out water was demonstrated by the formation of diphenyl urea when attempts were made to prepare the phenyl urethane. To eliminate the possibility that some 2-methyl pentanol-1-one-4 might be present, the product was oxidized in good yield to hexandione-2,5, which was identified by derivatization as the semicarbazone and the 2,4-dinitrophenylhydrazone. Had the attack of the acetoacetic ester anion been to any extent at the secondary epoxide carbon, the same degradation should have formed some alpha-methyllevulinic acid. None could be isolated.

The results of Wolff-Kishner reduction of this lactone indicated, although not certainly, that the reduction of the carbonyl group proceeded without cleaving the lactone. This lactone underwent "acidic" cleavage with sodium tertiary butoxide in slight yield to give 15% valerolactone, although considerable resinous material was formed. Both these results

indicate that alpha-acetolactones are much more stable toward bases than toward acids.

With styrene oxide the product, as far as could be ascertained, contained none of the product predicted by electronic considerations, but was entirely alpha-aceto-gamma-phenyl-gamma-butyrolactone resulting from the attack of the acetoacetic ester anion at the terminal epoxide carbon. No consideration seems to have been given in published reports to the steric effects of neighboring groups on the reactivity of epoxides and the direction of ring opening. The use of Fischer-Hirschfelder models indicates that the phenyl ring in styrene oxide can oscillate through an approximately 300° range, and only at one extreme of the oscillation would it be possible for an anion as large as that of acetoacetic ester to react at the secondary epoxide carbon. Smaller anions such as the methoxide and phenoxide ions would be expected to react much more readily at the secondary carbon, and such is the case. Swern reported that the methoxide ion reacts almost entirely at the secondary carbon (81). Guss reported that the bulkier phenoxide ion reacts 70% at the secondary carbon and 30% at the primary carbon (80), while Russell reported that the malonic ester anion reacts entirely at the terminal carbon (79) as has

been found to be the case with acetoacetic ester.

The structure of the reaction product was established by decarboxylation to 1-phenyl-pentanol-1-one-4. This product was the most difficult to prepare in a pure state of any of the liquids investigated, showing to a marked extent the analytical difficulties noted by other workers in the preparation of pure gamma-ketoalcohols (94, 95, 96). It also showed little typical carbonyl reactivity. Helferich, in a series of papers (121), established the fact that gamma-hydroxy aldehydes normally exist almost entirely in a furanose ring form. Gamma-ketoalcohols would likewise be expected to readily cyclize, sterically hindering the carbonyl carbon, explaining the lack of iodoform reaction and the slow formation of carbonyl derivatives. An oily phenyl hydrazone was formed after two days. No semicarbazone was formed after one week's standing. The Wolff-Kishner degradation step conclusively demonstrated the presence of the carbonyl group, although the reaction was carried out as quickly as possible after formation of the ketoalcohol to minimize the effect of cyclization. The above effect was expected, but the related problem of dimerization was totally unexpected. This will be discussed further with reference to the degradation of the reaction products

of butadiene monoxide and acetoacetic ester.

The structure of the 1-phenyl-pentanol-1-one-4 was established by two methods. The most direct was oxidation to phenacyl acetone, which is reported to form a semicarbazone with a melting point of 191° (124). This product readily formed a semicarbazone, but successive recrystallizations gave continually ascending melting points, ending with a product giving the same melting point as and analyzing closely for hydrazodicarbonamide (123). A search of the literature revealed that Helberger (106) had found phenacyl acetone to be useful in derivatizing primary amines through formation of N-substituted 2-methyl-5-phenyl-pyrroles. The aniline and phenylene diamine derivatives were readily prepared with the reported melting points. For further corroboration, phenacyl acetone was prepared by Helberger's method (the Friedel-Crafts reaction of levulinyl chloride and benzene), and the same derivatives were prepared for authentic samples.

In the oxidation step, some benzoic acid was formed, but no alpha-phenyllevulinic could be isolated under conditions reported to give its phenylhydrazone. This would be the expected product, had any of the original lactone been the result of the attack of the acetoacetic ester anion at the terminal epoxide carbon.

The structure was also confirmed by Wolff-Kishner reduction of the 1-phenyl-pentanol-1-one-4 to 1-phenyl-pentanol-1. This alcohol had the reported physical properties. The only derivative reported is the urethane, prepared with phosgene and ammonia. The alpha-naphthyl urethane was prepared, but the structure was more conclusively and simply established by oxidation to 1-phenyl-pentanone-1 (valerophenone) which was derivatized to give the semicarbazone with the reported melting point. Had any of the original product been formed by the attack of the acetoacetic ester anion at the secondary epoxide carbon, alpha-phenylvaleric acid should have been formed at this stage. None could be isolated. Both this oxidation and the previous one were carried out in acetone with permanganate. Limited solubility makes oxidation of such high molecular weight alcohols very slow in aqueous media.

Two attempts were made to oxidize this lactone to a ketoacid, with subsequent ring closure to an unsaturated lactone as the ultimate objective. The methods used were developed by McRae, Charlesworth, and Alexander (124) and applied by Russell and Vander Werf (79). Hot hypobromite solution gave 33% of an unstable brominated product which reddened very rapidly; and could not be purified. Acetoacetic ester itself gives

dichloroacetic acid, rather than chloroform with hypochlorite solutions (125), so that the bromine might be expected to react preferentially at the tertiary carbon, rather than with the freed hydroxyl group. Neutral permanganate left 16% unchanged lactone and 5% benzoic acid. Both methods resulted in the formation of large amounts of tarry material.

With butadiene monoxide acetoacetic ester formed two isomeric products, alpha-aceto-beta-vinyl-gamma-butyrolactone and alpha-aceto-gamma-vinyl-gamma-butyrolactone, in approximately equivalent quantities. This could be interpreted to indicate that the vinyl group and the hydrogen atom have very nearly the same electronegativities. The use of Fischer-Hirschfelder models again indicated that attack at the secondary epoxide carbon is sterically much more difficult than at the primary carbon. Through at least one third of the range of oscillation of the vinyl group, reaction would be impossible. Although Bartlett and Ross (50) made no quantitative analysis, they indicated that the major portion of the product of the base catalyzed reaction of butadiene monoxide with methyl alcohol was due to attack of the methoxide ion at the secondary carbon. It is a little difficult to correlate these results with Swern's finding that the slightly larger

alloxide ion attacked almost entirely at the secondary carbon (81). Perhaps the answer may be that the alloxide ion is more nucleophilic than the methoxide ion, and hence more influenced by the electron density of the attacked carbon atom. It is also difficult to explain Russell and Vander Werf's finding (79) that the malonic ester anion attacked solely at the primary carbon. In any case, there is enough experimental data available now to demonstrate that in base catalyzed reactions of epoxides, steric factors are at least as important as electronic considerations. It is, however, interesting to note that the heat of reaction was highest in this case, when the acetoacetic ester anion was able to react at a highly electrophilic carbon atom.

The structures of the two isomeric lactones were established by decarboxylation to hepten-1-ol-3-one-6 and 2-vinyl-pentanol-1-one-4. These products were difficult to obtain in analytical purity, as were the other gamma-ketoalcohols. The most surprising phenomenon of the entire problem was a 30° jump in the boiling point of these products after standing overnight. They also became insoluble in water after standing, but were soluble in 5% hydrochloric acid. When they

were displaced from the acid solution with potassium carbonate, the original ketoalcohols were recovered.

A search of the literature revealed that Stevens and Stein (96) had noted similar phenomena with 3-chloro-pentanol-1-one-4 and 3-bromo-pentanol-1-one-4, and were able to produce a similar effect by the action of catalytic amounts of hydrogen chloride on pentanol-1-one-4 itself. They proposed an explanation based on dimer formation by splitting out water between one molecule of the furanose ring form of the gamma-ketoalcohol and one molecule of the open chain form, which would require the presence of one free methyl-carbonyl group. The high boiling products of this research did not form carbonyl derivatives under the usual conditions, and did not give the iodoform test, which would indicate that these gamma-ketoalcohols may have dimerized by loss of water between two molecules of the cyclic form. A crude molecular weight determination in camphor indicated that the product had a molecular weight of about 200. Such a dimer would have a molecular weight of 238. Three attempts to obtain an analytical specimen of this higher boiling material yielded in each case products too low in carbon content, indicating contamination with some of the monomeric form.

In subsequent operations the ketoalcohols were degraded without isolation to hepten-1-ol-3 and 2-vinyl-pentanol-1 by Wolff-Kishner reduction. These alcohols were then hydrogenated catalytically over platinum to heptanol-3 and 2-ethyl-pentanol-1. Fractionation of the normal mixture gave equal quantities of the two alcohols. The two alcohols were obtained in 67% overall yield from the original lactones, and no "a priori" reason can be given for preferential reaction of either product in any of the degradation steps; so the presence of nearly equal quantities of the two isomeric lactones in the original mixture is at least reasonably well established. The 2-ethyl-pentanol-1 was identified as the 3-nitrophthalate, and the structure was confirmed by oxidation to 2-ethyl-pentanoic acid, which was identified as the amide and the anilide. No derivatives are reported for heptanol-3, although considerable work has been done with it. All the usual alcoholic derivatives of the heptyl alcohols are quite low melting and heptanol-3 appears to possess this property to a marked degree. Attempts were made to prepare crystalline derivatives with no success. Heptanol-3 is, however, readily oxidized to heptanone-3 which was identified as the semicarbazone.

Hydrogenation of the normally mixed vinyl-butyrolactones gave 76% of the expected saturated lactones, and also 14% of heptanone-2 resulting from cleavage and decarboxylation of alpha-aceto-gamma-vinyl-gamma-butyrolactone. It is interesting to note that all the cleavage apparently occurred with the lactone containing an allylic oxygen. Russell and Vander Werf (79) observed a similar cleavage on hydrogenation with gamma-vinyl-gamma-butyrolactone.

During the course of the research, alpha-carbethoxy-gamma-valerolactone was prepared from propylene oxide and malonic ester, and alpha-carbethoxy-gamma-vinyl-gamma-butyrolactone from butadiene monoxide and malonic ester. A similar preparation with styrene oxide resulted in decarboxylation during distillation, and the formation of gamma-phenyl-gamma-butyrolactone. The direction of epoxide ring opening has already been investigated in these three cases (79, 124), although these intermediates had not been prepared.

The propylene oxide used in this work came from Eastman Kodak Company, Organic Chemicals Division, Rochester, New York. We are indebted to the Dow Chemical Company, Midland, Michigan for the samples of styrene oxide used, and to the Columbia Chemicals Division of the Pittsburgh Plate Glass Corporation,

Pittsburgh, Pennsylvania for most of the butadiene monoxide. Since the latter compound was removed from commercial production in 1948, it was necessary to synthesize some of it. The reported methods in the literature include epoxidation with perbenzoic acid in ethyl chloride (69), and chlorohydrination followed by epoxidation with sodium hydroxide (73, 78). An attempt was made at direct epoxidation with peracetic acid using the method of Findley (126). No epoxide could be isolated. The reaction may have gone further to the hydroxyacetate or diacetate.

Petrov (78) applied chlorohydrination using the chlorourea method of Detoeuf (127) as modified by Lichosherstov (128). Attempted duplication of this method in a stoppered, shaken bottle resulted in an explosion; so the method was adapted to a stirred flask, and kept at about two-thirds of an atmosphere pressure by venting through a column of mercury. The yield was 34% of crude chlorohydrin, compared with 40% reported by Petrov.

Attempts to duplicate Kadesch's procedure (78) were entirely unsuccessful. Running the reaction under slight pressure and recondensing all the butadiene resulted in 30% yields, compared to the 52% reported by Kadesch. Although this method gave slightly lower

yield, it was preferable because of the shorter time involved, since calcium hypochlorite was readily available and the chlorourea had to be prepared. The product was also much more readily purified, since no acid other than carbon dioxide was introduced. This was very evident in the final distillation of the chlorohydrin. The chlorourea method left a tarry residue which was very difficult to remove, while the calcium hypochlorite method left a residue which was water soluble (largely dichlorohydrin).

PART IV

SUGGESTIONS FOR FURTHER INVESTIGATION

The obvious next step in this work should be an attempt to introduce an alpha-beta double bond in the alpha-aceto-gamma-lactones. Such a compound would appear to have the requisite structure for high antibiotic activity. The most promising route appears to be via halogenation at the tertiary carbon. Buchman (89) has reported the preparation of alpha-chloro-alpha-aceto-gamma-butyrolactone in good yield from the action of sulfuryl chloride on alpha-aceto-gamma-butyrolactone. Since this product would be an alpha-chloro-ketone, it might be quite resistant to hydrolysis, but it would be well worth attempting the removal of hydrogen chloride with some mild reagent such as pinene or pyridine.

If this route did not work, the preparation of such a compound by the Knoevenagel condensation of hydroxyacetaldehyde and acetoacetic ester appears to hold promise. The recent commercial appearance of dimethyl chloroacetal (General Aniline and Film Corporation, New York) provides a newly available route for the preparation of hydroxyacetaldehyde (129). Salicylaldehyde has been reported to condense smoothly in excellent yield with acetoacetic ester with piperidine as a catalyst (85), to form 3-acetocoumarin which has been shown to exhibit differential growth inhibitory

activity. A similar product with hydroxyacetaldehyde should be less toxic and as pharmacologically active. Malonic aldehyde, which is reported to exist largely as beta-hydroxy-acrolein (130), should also give an interesting product, but no good method of preparation has been reported.

Geiger and Conn (53) found that with alpha-beta-unsaturated ketones, a conjugated phenyl group increased the antibiotic activity, and direct connection of the phenyl group to the carbonyl group gave maximum activity; e.g. the following ketones showed the indicated order of antibiotic activity: acrylophenone > benzalacetone > mesityl oxide. Such a structure might be introduced into a lactonic compound by replacing ethyl acetoacetate with ethyl benzoylacetate. Two good syntheses for this compound have been published in Organic Syntheses (131).

The problem of the dimerization of gamma-keto-alcohols should be worth investigating for accurate determination of structure, and for the light it might throw on biological disaccharide formation.

This work has done nothing to clarify the mechanism of acid catalyzed condensations with allylic epoxides. The problem could be settled by the reaction of an optically active allylic epoxide with an acid. If the

S_N1 mechanism is correct, racemization should occur. If the S_N2 mechanism is correct, optical activity should be retained. It should be possible to prepare an optically active substituted styrene oxide. Another perhaps simpler approach would be through the reaction of a cyclic allylic epoxide, such as cyclopentadiene monoxide with hydrochloric acid. If the S_N1 mechanism prevails, two chlorohydrins should be obtained. Since they would be cis-trans isomers, their physical properties should differ enough to provide ready separation. If the S_N2 mechanism prevails, only the trans isomer should be obtained.

The real crux of most epoxide problems, and the reason for the confusion prevailing in the literature, lies in the lack of a quantitative method of separating or analyzing a mixture of primary and secondary alcohol isomers. In nearly all reactions of epoxides, one or both are formed. Surely some such analysis could be developed.

One of the earliest preparations of butadiene monoxide was by direct epoxidation with perbenzoic acid (69). Surprisingly, Pummerer and Reindel found that the second double bond could be epoxidized only with great difficulty. With chlorohydrination methods,

the chief defect is formation of large quantities of the dichlorohydrin. Perbenzoic acid is quite expensive, but direct epoxidation by air with benzaldehyde as a catalyst is not. This reaction appears to have been tried only with oleic acid (132). While it doubtless could not compete commercially with silver catalyzed production of epoxides from air and olefins, this method should make a useful laboratory tool and its investigation with lower olefins should be worthwhile. With conjugated diolefins like butadiene, it might well be preferable to silver catalysis. Difficulty of epoxidation of the second double bond with silver catalysts should also be investigated.

Only 17 of the 40 possible heptyl alcohols have been reported, and of these 17, many have not been derivatized. The problem of the preparation of these alcohols and their derivatization has been started by the class in organic preparations at Geneva College.

BIBLIOGRAPHY

(1) Rabourdin, Ann., 52, 392 (1844)

(2) Gradzhi, Ber., 17, 1369 (1884)

(3) Wolff, Ann., 229, 249 (1885)

(4) Fisher, Ber., 23, 2625 (1890)

(5) Saytzeff, Ann., 179, 300 (1875)

(6) Fittig and Mielch, Ann., 180, 68 (1875)

(7) Pelouze, Ann., 7, 43 (1833)

(8) Henry, Ber., 7, 753 (1874)

(9) Fittig, Ann., 200, 61 (1879)

(10) Tiemann, Ber., 26, 1595 (1893)

(11) Patterson, J. Am. Chem. Soc., 55, 3905 (1933)

(12) Erlenmeyer, Ber., 13, 303 (1880)

(13) Bredt, Ber, 13, 748 (1880)

(14) Richardson, "The Foundations of Stereochemistry", American Book Co., New York (1901)

(15) Baeyer, Ber., 18, 2277 (1885)

(16) Darlington and Denison, Phys. Rev., 57, 128 (1940)

(17) Fittig, Ber., 16, 373 (1883)

(18) Einharn, Ber., 16, 2208, 3001 (1883)

(19) Steadman, U. S. Patent 2,424,589

(20) Moncrieff, Am. Perfumer Essent. Oil Rev., 49, 42 (1947)

(21) Chen and Elderfield, J. Pharmacol. Exp. Therap., 70, 338 (1940)

(22) Ott, Houben-Weyl's "Die Methoden Organischen Chemie", Leipzig, 1930, Vol. III, p. 682

(23) Fourneau, Produits pharm., 1, 126, 154 (1943)

(24) Veldstra and Havinga, Enzymologia, 11, 373 (1945)

(25) Broderson and Kjaer, Acta Pharmacol. Toxicol., 2, 109 (1946)

(26) L. Ruzicka et al., Helv. Chim. Acta, 24, 716 (1941); 25, 79 (1942); 27, 988 (1944)

(27) Wieland, Hesse and Hüttel, Ann., 524, 203 (1936)

(28) (a) Späth and Kuffner, Monatsh., 69, 75 (1936)
(b) Späth, Ber. 70A, 83 (1937)

(29) Kuhn and Jerchel, Ber., 76, 413 (1943)

(30) Werder, E. Merck's Jahresber., 50, 88 (1936)

(31) E. Merck's Jahresber., 35, 3 (1921)

(32) Mannich, Therap. Monatsh., 1913, 124; Ber. deut. pharm. Ges., 19, 388 (1909)

(33) Campbell, Link et al., J. Biol. Chem., 119, 269 (1937); 136, 47 (1940); 138, 121, 513 (1941)

(34) Borsche and Peitzch, Ber., 63, 2414 (1930)

(35) Clemo et al., J. Chem. Soc., 1929, 2368; 1930, 1110, 2579

(36) Ruzicka and Eichenberger, Helv. Chim. Acta, 13, 1117 (1930)

(37) Rosenmund and Schapiro, Arch. Pharm., 272, 313 (1934)

(38) Karrer, Gehrkens and Heuss, Helv. Chim. Acta, 9, 446 (1926)

(39) Alsberg and Black, U. S. Dept. Agr. Bur. Plant Ind. Bull. No. 270 (1913)

(40) (a) Waksman et al., J. Bact., 45, 233 (1942)

(b) Raistrick et al., Lancet, 245, 625 (1943)

(c) Raistrick et al., Biochem. J., 29, 300, 871, 1300 (1935)

(41) (a) The Chemistry of Penicillin, Princeton Univ. Press, Princeton, New Jersey (1948)

(b) Science, 105, 657 (1947)

(42) Schmidt, Z. Immunitätsforsch., 102, 233 (1942)

(43) Kögl, Naturwissenschaften, 30, 392 (1942)

(44) Veldstra and Havinga, Rec. trav. chim., 62, 841 (1943)

(45) Medawar, Robinson and Robinson, Nature, 151, 195 (1943)

(46) Kuhn et al., Naturwissenschaften, 31, 468 (1943); Ber., 76, 413 (1943)

(47) Cameron, J. Phys. Chem., 14, 422 (1910)

(48) Sigmund, Biochem. Z., 62, 339 (1914)

(49) Macht and Kranz, J. Pharmacol. Exp. Therap., 31, 11 (1927); J. Amer. Pharm. Assoc. Sci. Ed., 16, 210 (1927)

(50) Bartlett and Ross, J. Amer. Chem. Soc., 70, 926 (1948)

(51) Veldstra and Havinga, Enzymologia, 11, 97, 137 (1944)

(52) (a) Lauger, Martin and Müller, Helv. Chim. Acta, 27, 892 (1944)

(b) Chem. Eng. News, 27, 1942 (1949)

(53) Geiger and Conn, J. Am. Chem. Soc., 61, 112 (1945)

(54) Cavallito and Haskell, J. Am. Chem. Soc., 67, 1991 (1945)

(55) Mendez, J. Pharmacol. Exp. Therap., 81, 151 (1944)

(56) Wurtz, Ann., 110, 126 (1859)

(57) Organic Syntheses, Coll. Vol. I, John Wiley & Sons, New York (1943), 2nd Ed., p. 185.

(58) Prileshajew, Ber., 42, 481 (1909)

(59) McBee, Hass, and Wiseman, Ind. Eng. Chem., 37, 432 (1945)

(60) Greene, Compt. rend., 85, 624 (1877)

(61) Weitz and Sheffer, Ber., 54, 2327 (1921)

(62) (a) Darzens, Compt. rend., 139, 1214 (1904)

(b) Claisen, Ber., 38, 693 (1905)

(63) Widmann, Ann., 400, 104 (1913)

(64) Patterson and Capell, "The Ring Index", Reinhold Publishing Corp., New York (1940)

(65) Krassuski, J. Russ. Phys. Chem. Soc., 34, 307 (1902)

(66) Pariselle, Compt. rend., 150, 1344 (1910)

(67) Fourneau, Tiffeneau, Compt. rend., 140, 1595 (1905); 146, 697 (1908)

(68) Reference 57; page 494

(69) Pummerer and Reindel, Ber., 66B, 335 (1933)

(70) Winstein and Lucas, J. Am. Chem. Soc., 61, 1576 (1939)

(71) Grigsby et al., J. Am. Chem. Soc., 64, 2606 (1942)

(72) Newman and Vander Werf, J. Am. Chem. Soc., 67, 233 (1945)

(73) Kadesch, J. Am. Chem. Soc., 68, 41 (1946)

(74) Remick, "Electronic Interpretations of Organic Chemistry", John Wiley & Sons Inc., New York (1949) p. 66.

(75) Ingold, Chem. Revs., 15, 225 (1934)

(76) See, for example, Abderhalden, Eichwald, Ber., 51, 1318 (1918); Chitwood and Freure, J. Am. Chem. Soc., 68, 680 (1946)

(77) Winstein and Buckles, J. Am. Chem. Soc., 64, 2780 (1942)

(78) Petrov., J. Gen. Chem. (U.S.S.R.), 8, 131 (1938)

(79) Russell and Vander Werf, J. Am. Chem. Soc., 69, 11 (1947)

(80) Guss, C. O., University of Southern California, Private Communication, May 3, 1949

(81) Swern, Billen and Knight, J. Am. Chem. Soc., 71, 1152 (1949)

(82) Geuther, Jahresbericht über die Fortschritt der Chemie, 1863, 323

(83) Claisen, Ber., 38, 709 (1905)

(84) Knorr, Ber., 30, 2389 (1897)

(85) Knoevenagel, Ber., 31, 732 (1898)

(86) Traube and Lehman, Ber., 34, 1971 (1901)

(87) Kotz and Hofmann, J. prakt. Chem., 110, 101 (1925)

(88) Knunyantz, Chelintzev, and Osetrova, Compt. rend. acad. sci., (U.R.S.S.) (N.S.), 1, 312 (1934)

(89) Buchman, J. Am. Chem. Soc., 58, 1803 (1936)

(90) Carmack et al., J. Am. Chem. Soc., 68, 1220 (1946)

(91) Lund and Bjerrum, Ber., 64, 210 (1931)

(92) Smith, J. Chem. Soc., 1927, 1288

(93) Perkins and Stenhouse, J. Chem. Soc., 61, 72 (1892)

(94) Lipp and Scheller, Ber., 42, 1960 (1909)

(95) Wohlgemuth, Compt. rend., 159, 82 (1914)

(96) Stevens and Stein, J. Am. Chem. Soc., 62, 1045 (1940)

(97) Bischoff and Walden, Ber., 26, 1454 (1893)

(98) Gray, J. Chem. Soc., 79, 681 (1901)

(99) Armstrong and Robinson, J. Chem. Soc., 1934, 1650

(100) Schuette and Sah, J. Am. Chem. Soc., 48, 3165 (1926)

(101) Darapsky et al., J. prakt. Chem., [2], 147, 150 (1936)

(102) Fittig and Young, Ann., 216, 41 (1883)

(103) Rinkenback, Ind. Eng. Chem., 19, 474 (1927)

(104) Huang-Minlon, J. Am. Chem. Soc., 68, 2487 (1946)

(105) Arndt et al. Ber., 69, 2379 (1936)

(106) Helberger, Ann., 522, 269 (1936)

(107) (a) Weltner, Ber., 17, 72 (1884)

(b) Ruhemann, J. Chem. Soc., 85, 1455 (1904)

(108) Levene, Mikeska, J. Biol. Chem., 70, 355 (1926)

(109) Shriner and Turner, J. Am. Chem. Soc., 52, 1269 (1930)

(110) Layraud, Bull. soc. chim. France, [3], 35, 224 (1906)

(111) (a) Pickard and Yates, J. Chem. Soc., 95, 1017 (1909)

(b) Levene and Marker, J. Biol. Chem., 88, 53 (1930)

(112) Sherrill, J. Am. Chem. Soc., 52, 1990 (1930)

(113) Dillon and Lucas, J. Am. Chem. Soc., 50, 1711 (1928)

(114) Morgan, Hardy, Proctor, Chemistry and Industry, 51T, 7 (1932)

(115) Levene et al., J. Biol. Chem. 115, 401 (1936)

(116) Kenyon and Snellgrove, J. Chem. Soc., 1925, 1169

(117) Reference 57, p. 168

(118) Reichstein and Trivelli, Helv. Chim. Acta, 15, 259 (1932)

(119) Rasetti, Bull. soc. chim. France, 33, 685 (1905)

(120) Michael, J. Am. Chem. Soc., 41, 411 (1919)

(121) Helferich, Ber., 52, 1123, 1800 (1919; 54, 930, 2640 (1921); 55, 702 (1922); 56, 2088 (1923); 57, 1911 (1924)

(122) Finxi, Gazz. chim. ital., 42, ii, 356 (1912)

(123) Thiele, Ann., 270, 45 (1892)

(124) McRae, Charlesworth, and Alexander, Can. J. Research, 21B, 1 (1943)

(125) Hurd and Thomas, J. Am. Chem. Soc., 55, 1646 (1933)

(126) Findley, Swern, and Scanlan, J. Am. Chem. Soc., 67, 412 (1945)

(127) Detoeuf, Bull. soc. chim. France, [4], 31, 102, 169 (1922)

(128) Lichosherstov, J. Gen. Chem. (U.S.S.R.), 8, 131 (1938)

(129) Hartung, J. Am. Chem. Soc., 49, 2520 (1927)

(130) Claisen, Ber., 36, 3668 (1903)

(131) (a) Shriner, Schmidt, and Roll, Organic Syntheses, Coll. Vol. II, John Wiley and Sons, New York (1943), p. 266

(b) McElvain and Weber, ibid., 23, 35 (1943)

(132) Swern, Findley, and Scanlan, J. Am. Chem. Soc., 66, 1925 (1944)